AMERICAN HEART JOURNAL

February 1958
Volume 55 No. 2

Prevention of the "Phosphate-Steroid-Cardiopathy" by Various Electrolytes

H. Selye, M.D., and R. K. Mishra, M.D., Montreal, Canada

The toxicity of orally administered phosphates is greatly increased by desoxycorticosterone, in the rat. For example, doses of NaH_2PO_4 which are normally well tolerated produce a rapidly fatal nephrocalcinosis in rats simultaneously treated with desoxycorticosterone acetate.[1] Recently, it has also been observed that infarct-like, massive patches of cardiac necrosis can be regularly produced by combined treatment with phosphates and certain steroids, although such changes do not develop when either the phosphates or the steroids are given alone.[2] This singular "phosphate-steroid-cardiopathy" has been the subject of extensive studies during the last year, because it was felt that this newly discovered interaction between phosphates and steroids may help to elucidate some fundamental problems of cardiac physiology, including the biochemical basis of those cardiac infarctions not due to demonstrable, acute vascular obstructions. Like true cardiac infarcts, the individual lesions of the phosphate-steroid-cardiopathy consist of massive, necrotic patches, within whose limits the muscle fibers are gradually absorbed and replaced, first by histiocytes and polymorphonuclear cells, later by connective tissue. The infarctoid lesions of the phosphate-steroid-cardiopathy also resemble spontaneous infarcts of the heart in that they can be elicited by exposure to sudden, stressful neuromuscular exertion.[3] On the other hand, these experimental lesions differ from the usual spontaneous infarcts, inasmuch as they are not due to histologically detectable vascular occlusions. The production of any cardiac infarct depends upon the relationship between the metabolic requirements and the blood supply of the heart. Hence, it is possible (although still unproved) that combined treatment with steroids and phosphates may increase the requirements to a point where—especially during periods of stress—even the normal supply becomes insufficient.

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.

These experiments were supported in part by the Medical Research Board, Office of the Surgeon General, Department of the United States Army, Contract No. DA-49-007-MD-186, and in part by The Squibb Institute for Medical Research.

Received for publication Dec. 2, 1957.

In most of the initial investigations concerning the pathogenesis of the phosphate-steroid-cardiopathy, 2α-methyl-9α-chlorocortisol (Me-Cl-COL) was used; this steroid proved to be particularly effective in producing cardiac necrosis when given in combination with NaH_2PO_4.[2,4]

Subsequent to these first observations our most pressing task was to prove that it is really the PO_4 ion that is of importance in the conditioning of the cardiac muscle for the necrotizing actions of steroids. Experiments on rats indicated that both the monobasic and the dibasic sodium phosphates are highly active in producing such myocardial lesions, when given conjointly with Me-Cl-COL. It was assumed, therefore, that the lesions are not due merely to a change in pH induced either by the acid or the basic phosphate. Since, on the other hand, Me-Cl-COL given with equimolecular amounts of sodium chloride also failed to produce the characteristic myocardial necroses, it became clear that, likewise, the sodium ion in itself cannot be the responsible conditioning factor. From this it was concluded that, for the production of the phosphate-steroid-cardiopathy, the phosphate ion is the essential part of NaH_2PO_4.[4]

In an effort to clarify the specificity of the necrosis-eliciting mechanism, rats were briefly pretreated with subthreshold amounts of Me-Cl-COL plus NaH_2PO_4. Although this pretreatment produced few or no cardiac lesions, subsequent exposure to the stress of neuromuscular effort (induced by strapping the rats onto a board) resulted in severe and extensive cardiac necroses in 100 per cent of the experimental animals. Indeed, even in rats pretreated only with Me-Cl-COL without phosphate supplements, such neuromuscular exertion was capable of producing cardiac lesions which were marked, although less constant and less severe.[3] It might have been thought that neuromuscular exertion acts specifically (not merely through its stress effect), but in rats similarly sensitized with subthreshold doses of Me-Cl-COL plus phosphate, a high incidence of massive myocardial necroses could be elicited also by bilateral vagotomy, hot or cold baths, multiple bone fractures, crushing of intestines, quadriplegia (subsequent to transection of motor nerves), or toxic doses of adrenaline.[5]

Although Me-Cl-COL is the most effective, several other steroids also proved to be capable of producing this type of cardiopathy. For example, 2α-methyl-9α-fluorocortisol (Me-F-COL) and the two corresponding, nonmethylated steroids (9α-chlorocortisol and 9α-fluorocortisol) are likewise very effective in this respect. Among those examined, the only halogenated corticoid devoid of this activity is triamcinolone, a highly active glucocorticoid which possesses little or no mineralocorticoid potency. On the other hand, cortisone, a glucocorticoid with little mineralocorticoid activity, is at least as effective in producing phosphate-steroid-cardiopathy as is desoxycorticosterone, although the latter is considerably more mineralocorticoid than the former. In view of these findings, it is not yet clear whether there is any relationship between the classical mineralocorticoid potency and the ability of steroids to produce cardiac necroses when given in combination with phosphates.[6] Cortisol (hydrocortisone) is comparatively ineffective in producing this cardiopathy, even when given in combination with phosphates; yet, in rats pretreated with cortisol and phosphate, neuromuscular exertion elicits particularly severe cardiac necroses.[7] This suggests that combined treatment

with phosphates and certain steroids may be less effective in producing myocardial necroses than in conditioning the heart for the subsequent detrimental effect of a stressful experience. However, further experiments will be required before this can be considered proved.

The biologic and, particularly, the medical implications of all these observations are largely dependent upon the demonstration that the production of such cardiac necroses is not merely a species-specific reaction type peculiar to the rat. It is significant, therefore, that similar cardiac lesions have been produced also by Me-Cl-COL plus NaH_2PO_4 in the guinea pig, rabbit, dog,[8] and hamster.[9] Since the principal glucocorticoid of man is cortisol, it is especially noteworthy that extensive myocardial necroses can be produced likewise in primates (rhesus monkeys) by combined treatment with cortisol acetate and NaH_2PO_4.[10] This makes it probable that the cardiac muscle of man is also sensitive to this type of action.

Nephrocalcinosis is not necessarily associated with the infarctoid cardiopathy. It occurs in rats, but not in guinea pigs or rabbits, in which cardiac necroses are produced by Me-Cl-COL plus phosphates.[10]

Almost 30 years ago one of us noted that certain steroids of the vitamin-D group may produce cardiac necroses with tissue calcification, in the rat.[11,12] The question arose whether this type of change could be influenced also by excess dietary phosphates. Normally, dihydrotachysterol produces only calcification and necrosis of the cardiac muscle, and no inflammatory reaction; however, simultaneous treatment with NaH_2PO_4 transforms the character of these lesions, so that a suppurative, acute myocarditis results.[13] From this it appears that even acute inflammatory changes may be produced in the myocardium by combined treatment with certain steroids and phosphates.

More recently, our attention was directed to the possibility of preventing the phosphate-steroid-cardiopathy and the accompanying nephrocalcinosis. It was found that oral administration of large doses of KCl offers virtually complete protection against both the cardiac lesions and the renal calcification normally produced by treatment with NaH_2PO_4 plus Me-Cl-COL.[14]

In this communication we intend to show that this effect of KCl is not specific, but may be duplicated by various other electrolytes, and by magnesium chloride in particular.

MATERIALS AND METHODS

Three experimental series were performed on a total of 29 groups, each consisting of 10 female Sprague-Dawley rats, with an average initial body weight of 96 grams (range: 85 to 111 grams).

Invariably, 2α-methyl-9α-chlorocortisol (Me-Cl-COL) was administered in the form of a microcrystal suspension of its acetate, at the dose of 50 μg in 0.2 ml. of water, subcutaneously, once daily.

The phosphates employed to produce the phosphate-steroid-cardiopathy were: monosodium dihydrogen phosphate, $NaH_2PO_4 \cdot H_2O$ (reagent, Fisher) and disodium monohydrogen phosphate, Na_2HPO_4 (reagent, Fisher).

The following compounds were tested with regard to their possible inhibitory effect upon the syndrome: sodium chloride, NaCl (U.S.P., Brickman); potassium chloride, KCl (reagent, Fisher); potassium bisulfate, $KHSO_4$ (reagent, Fisher); potassium sulfate, K_2SO_4 (N.F. powdered, Mallinckrodt); potassium acetate, CH_3COOK (reagent, Merck); magnesium chloride, $MgCl_2 \cdot 6H_2O$

Fig. 1.

Fig. 2.

Fig. 1.—Macroscopic aspect of the phosphate-steroid-cardiopathy in a rat of Group I of the third experimental series. The white necrotic patches are clearly visible (bottom). Compare with the normal appearance of the heart of an animal from Group VI of the third experimental series in which the cardiopathy was inhibited by $MgCl_2$.

Fig. 2.—General aspect of a necrotic patch in the heart of a rat with the phosphate-steroid-cardiopathy (from Group I of the first experimental series). A dark line of necrotic tissue separates the healthy muscle (top) from the center of the lesion where the muscle fibers have already been largely replaced by histiocytes and polymorphonuclear leukocytes (hematoxylin-phloxine × 75).

Fig. 3.

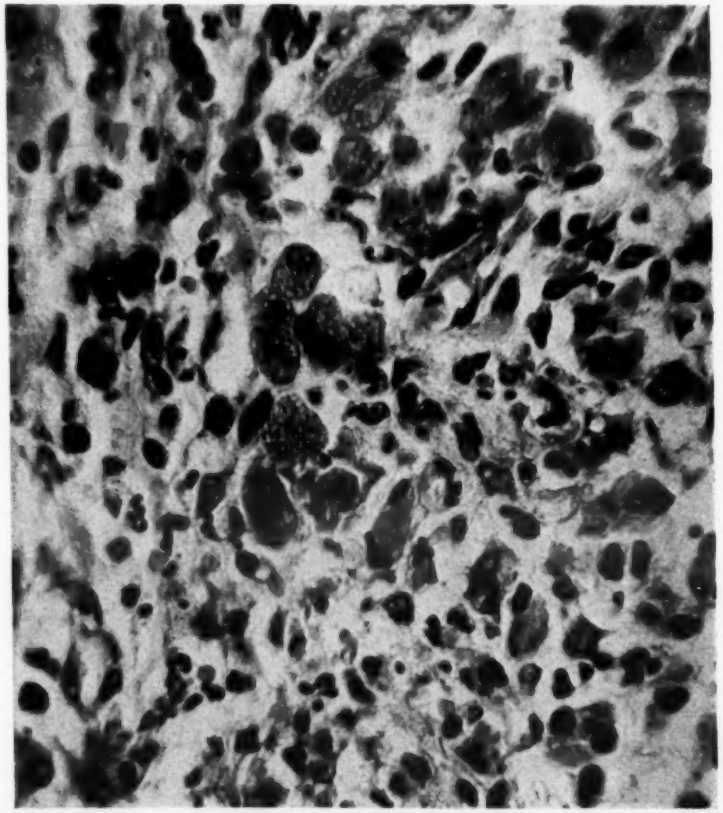


Fig. 4.

Fig. 3.—Very recent necrotic patch in the same heart. The muscle fibers have lost their normal structure, but are still distinguishable. Only an occasional polymorphonuclear leukocyte has invaded the region (hematoxylin-phloxine × 480).

Fig. 4.—An older necrotic focus in the same heart. Here, only a few muscle fibers are still distinguishable among the numerous histiocytes, polymorphonuclear cells, and young connective-tissue cells which occupy the field (hematoxylin-phloxine × 480).

(reagent, Merck); calcium chloride, $CaCl_2 \cdot 2H_2O$ (C. P., Baker); ammonium chloride, NH_4Cl (reagent, Nichols); glucose (dextrose anhydrous, Merck).

Since the doses and routes of administration of these compounds were not always the same, these details will be discussed separately in the description of the three experimental series.

Throughout the experiment, all the animals were maintained exclusively on "Purina Fox Chow." Wherever indicated, the water turnover was measured daily. The mean water intake over the entire experimental period (with its standard error) is listed in the tables.

The incidence (per cent positive) and grade (intensity in terms of an arbitrary scale of 0 to 3) of both the cardiopathy and the nephrocalcinosis were appraised on the fresh specimens with the aid of a dissecting microscope. These findings were verified in dubious cases on two histologic sections through each specimen. Hematoxylin-phloxine was used for appraisal of general structure, and von Kossa's silver nitrate method for the histochemical demonstration of calcium. The macroscopic aspect of a typical "Grade 3" cardiac lesion is illustrated in Figs. 1-4, together with several characteristic types of histologic structure.

Since intense catabolism is also a typical feature which accompanies the phosphate-steroid-cardiopathy, the final mean body weights (with standard errors) of all groups are likewise listed in our tables. As the initial body weight was the same in all groups, the change in weight that occurred during the experiment can be easily calculated.

RESULTS

First Experimental Series.—Six groups of rats were treated with 50 μg of Me-Cl-COL, subcutaneously, once daily, and with 300 mg. of NaH_2PO_4 in 2 ml. of water, administered by stomach tube, twice daily. In addition, the controls (Group I) received 2 ml. of water, twice daily, while the others were given NaCl (Group II), KCl (Group III), $KHSO_4$ (Group IV), K_2SO_4 (Group V), or $MgCl_2$ (Group VI), always at the dose level of 300 mg. in 2 ml. of water, twice daily, by stomach tube.

The experiment was terminated on the twelfth day of treatment and the results are summarized in Table I.

TABLE I. FIRST EXPERIMENT: EFFECT OF VARIOUS ELECTROLYTES UPON THE SYNDROME INDUCED BY Me-Cl-COL AND NaH_2PO_4

GROUP	TREATMENT*	FINAL BODY WEIGHT (GM.)	CARDIAC NECROSIS		NEPHROCALCINOSIS		MORTALITY (PER CENT)
			INCIDENCE (PER CENT)	GRADE (0–3)	INCIDENCE (PER CENT)	GRADE (0–3)	
I	None	100 ± 7.5	100	2.5 ± 0.3	100	2.9 ± 0.06	100
II	NaCl	103 ± 4.2	0	0	0	0	70
III	KCl	104 ± 3.8	10	0.2 ± 0.2	0	0	10
IV	$KHSO_4$	97 ± 0	0	0	0	0	90
V	K_2SO_4	113 ± 3.4	0	0	30	0.5 ± 0.3	10
VI	$MgCl_2$	107 ± 5.5	0	0	40	0.4 ± 0.18	20

*In addition to the treatments listed in this column, the animals of all groups received 50 μg of Me-Cl-COL plus 600 mg. of NaH_2PO_4, as outlined in the text.

It is evident that both the cardiopathy and the nephrocalcinosis were significantly inhibited by all the electrolyte solutions, but only KCl, K_2SO_4 and $MgCl_2$ succeeded in reducing the mortality rate markedly.

In order to avoid the potentially damaging effect of four daily gavages (two of NaH_2PO_4 plus two of the prophylactically administered electrolyte solutions), and in order to verify the possible prophylactic effect of additional solutes, a more extensive, second experimental series was performed under improved conditions.

Second Experimental Series.—Nine groups of rats were treated with 50μg of Me-Cl-COL, subcutaneously, once daily, and with 300 mg. of NaH_2PO_4, in 2 ml. of water, administered by stomach tube twice daily. In addition, the controls (Group I) received 2 ml. of water, orally, twice daily, while others were given glucose (Group II), NaCl (Group III), K-acetate (Group V), or $MgCl_2$ (Group VI), always at the dose of 300 mg. in 2 ml. of water, twice daily, by stomach tube. However, in these groups, the test solutions were mixed with the phosphate solution before administration, so that a total volume of 4 ml. was given orally, twice daily. Instead of drinking water, the remaining groups received NaCl (Group IV), $MgCl_2$ (Group VII), $CaCl_2$ (Group VIII), or NH_4Cl (Group IX), in 1 per cent aqueous solutions, *ad libitum*, throughout the experiment. In order to observe any possible diuretic effect of these solutions, the water intake was measured daily.

The experiment was terminated on the sixth day of treatment, and the results are summarized in Table II.

Four rats in Group V, and five rats in Group IX died during the first three days of the experiment (without any evidence of cardiac or renal lesions), presumably as a result of potassium acetate and ammonium chloride intoxication, respectively. However, it is clear that NaCl, $MgCl_2$, and the potassium salt were again effective in significantly inhibiting various manifestations (cardiopathy, catabolism, mortality) normally produced by Me-Cl-COL-plus-phosphate treatment. This was so, irrespective of whether the electrolytes were given by gavage or in the drinking fluid. $CaCl_2$ and NH_4Cl (which were too toxic to be administered in the form of concentrated solutions by gavage) likewise exerted a protective effect against the phosphate-steroid-cardiopathy, when administered in the drinking fluid.

Significant inhibition of the nephrocalcinosis, on the other hand, was achieved only by the electrolytes that were given in high concentrations by gavage. Presumably, larger amounts of these substances are required for the prevention of calcification in the kidney than for protection against cardiac necrosis, catabolism, and mortality.

These findings suggest that the inhibition of the phosphate-steroid syndrome is shared by various electrolytes and does not represent a specific property of the potassium ion. On the other hand, comparable amounts of glucose actually aggravated both the cardiac necrosis and the nephrocalcinosis caused by Me-Cl-COL-plus-phosphate treatment. Additional experiments have shown that various other carbohydrates share this aggravating effect of glucose, but these will be described later in a separate publication. Here, we merely wish to call attention to the fact that, up to the present time, it was possible to prevent the phosphate-steroid-intoxication syndrome only with electrolyte solutions.

A third experimental series was then performed to confirm these findings and to determine the possible effect of mere variations in water intake.

TABLE II. SECOND EXPERIMENT: EFFECT OF VARIOUS ELECTROLYTES AND GLUCOSE UPON THE SYNDROME INDUCED BY Me-Cl-COL AND NaH_2PO_4

GROUP	TREATMENT*	FINAL BODY WEIGHT (GM.)	CARDIAC NECROSIS		NEPHROCALCINOSIS		MORTALITY (PER CENT)	WATER INTAKE (ML.)
			INCIDENCE (PER CENT)	GRADE (0–3)	INCIDENCE (PER CENT)	GRADE (0–3)		
I	None	80 ± 1.9	60	1 ± 0.37	100	1.3 ± 0.24	100	7 ± 1.1
II	Glucose, gavage	97 ± 3.0	90	2.7 ± 0.3	100	2.7 ± 0.21	60	20.2 ± 1.5
III	NaCl, gavage	110 ± 2.8	10	0.1 ± 0.1	10	0.1 ± 0.1	0	58.9 ± 3.3
IV	NaCl, drink	93 ± 1.9	40	0.4 ± 0.16	100	1.4 ± 0.16	0	49.3 ± 8.3
V	CH_3COOK, gavage	103 ± 3.3	20	0.2 ± 0.15	60	0.7 ± 0.21	40	59.8 ± 7.7
VI	$MgCl_2$, gavage	110 ± 3.4	0	0	0	0	0	35.8 ± 2.0
VII	$MgCl_2$, drink	96 ± 3.9	10	0.1 ± 0.1	90	1.2 ± 0.25	0	23.3 ± 2.3
VIII	$CaCl_2$, drink	100 ± 2.6	0	0	100	1.6 ± 0.16	10	23.5 ± 2.4
IX	NH_4Cl, drink	82 ± 3.6	10	0.12 ± 0.12	60	0.9 ± 0.3	50	14.3 ± 2.0

*In addition to the treatments listed in this column, the animals of all groups received 50 μg of Me-Cl-COL plus 600 mg. of NaH_2PO_4, as outlined in the text.

TABLE III. THIRD EXPERIMENT: EFFECT OF VARIOUS ELECTROLYTES AND CHANGES IN WATER INTAKE UPON THE SYNDROME INDUCED BY Me-Cl-COL AND NaH_2PO_4

GROUP	TREATMENT*	FINAL BODY WEIGHT (GM.)	CARDIAC NECROSIS		NEPHROCALCINOSIS		MORTALITY (PER CENT)	WATER INTAKE (ML.)
			INCIDENCE (PER CENT)	GRADE (0–3)	INCIDENCE (PER CENT)	GRADE (0–3)		
I	None	92 ± 5.1	100	2.4 ± 0.30	100	2.8 ± 0.07	78	21 ± 1.3
II	NaCl	97 ± 3.3	20	0.2 ± 0.15	10	0.11 ± 0.11	20	47.5 ± 3.8
III	KCl	113 ± 3	20	0.2 ± 0.15	0	0	0	40 ± 4.7
IV	$KHSO_4$	100 ± 2.5	10	0.1 ± 0.1	70	0.9 ± 0.23	0	30.5 ± 2.8
V	K_2SO_4	107 ± 2.8	10	0.1 ± 0.1	20	0.2 ± 0.13	0	38.4 ± 4.5
VI	$MgCl_2$	111 ± 2.4	0	0	0	0	0	35.1 ± 2.9
VII	$CaCl_2$	108 ± 3.6	10	0.11 ± 0.11	0	0	30	31.3 ± 4.0
VIII	H_2O deficiency	**	40	1.2 ± 0.34	90	1.2 ± 0.25	100	1.5 ± 0
IX	H_2O excess	87 ± 2.6	80	1.0 ± 0.25	100	2.8 ± 0.13	10	55.9 ± 2.0
X	None	95 ± 4.5	80	2.0 ± 0.5	100	2.5 ± 0.26	70	30.6 ± 3.5
XI	NH_4Cl	106 ± 4.1	0	0	60	0.57 ± 0.2	60	39.4 ± 5.3

*In addition to the treatments listed in this column, the animals of all groups received 50 μg of Me-Cl-COL plus 400 mg. of NaH_2PO_4 (Groups I-IX), or 400 mg. of Na_2HPO_3 (Groups X and XI), as outlined in the text.

**Since all animals in this group died, and most of them did so considerably before termination of the experiment, their final body weights would not be comparable to those of the other groups and have therefore not been listed.

Third Experimental Series.—Eleven groups of rats were treated with 50 μg of Me-Cl-COL, subcutaneously, once daily; in addition, Groups I-IX received 200 mg. of NaH_2PO_4 in 2 ml. of water, except for the rats in Group VIII (water deficiency), which were given the same amount of NaH_2PO_4 in 1 ml. of water, twice daily. This group was completely deprived of drinking water, except during the fourth and sixth days when water was allowed *ad libitum*. Conversely, in Group IX excess water was administered by stomach tube: 10 ml., four times daily during the first three days and 12 ml., four times daily during the rest of the experiment. Groups X and XI received 200 mg. of Na_2HPO_4, in 2 ml. of water, twice daily, by stomach tube. Dibasic sodium phosphate was administered in Group XI to prevent the invariably fatal acidosis that normally results from treatment with large doses of NH_4Cl, and in Group X for control purposes. The other electrolytes listed in Table III were mixed with the phosphate solution and also administered at the dose level of 200 mg. in 2 ml. of water, twice daily, as in the second experimental series.

The experiment was terminated on the eighth day of treatment and the results are summarized in Table III.

We note that, again, all the electrolytes exerted a pronounced protective effect against the cardiac manifestations of the phosphate-steroid syndrome; to a lesser extent they also diminished the nephrocalcinosis. Since most of the animals deprived of water died during the second half of the first week, the apparently protective effect of thirsting is meaningless. A great excess of water offered less protection against the cardiac necrosis than did any of the electrolyte solutions; it afforded no protection against nephrocalcinosis. Consequently, the smaller increase in voluntary water intake occasioned by the electrolytes could not be held responsible for their protective action.

DISCUSSION

It has long been known that cardiac necroses may develop in rats kept on potassium-deficient diets.[15,16,17] When it was later observed that the occasional production by desoxycorticosterone (without conditioning by phosphate) of microscopic foci of cardiac necrosis can be prevented by KCl, it was, of course, tempting to conclude that: "These experiments seem conclusive that deficit of potassium is the central feature of the cardiac lesions produced by prolonged injections of desoxycorticosterone acetate."[18] It should be kept in mind, however, that a systematic examination of numerous steroids has shown no close relationship between mineralocorticoid potency and the ability to produce cardiac necroses after conditioning with phosphate. In particular, short-term treatment with desoxycorticosterone (given with or without phosphate under conditions similar to those that prevailed in the present experimental series) proved to be comparatively ineffective in producing such cardiac lesions.[6] It is conceivable that both the sensitizing effect of phosphates and the protective action of the various electrolytes examined in the present experimental series act by influencing the potassium metabolism of the heart; but, at present, we have no objective evidence to substantiate such a hypothesis.

In any event, it is clear that various cations share with potassium the ability to protect the rat against the phosphate-steroid syndrome. Experiments are now under way to explore the possibility of preparing electrolyte combinations in which each ion would be present in amounts far below the toxic range, and yet contribute its share to the protective effect of the mixture.

SUMMARY

The massive cardiac necroses (as well as the nephrocalcinosis, catabolism, and high mortality rate) that are normally induced in the rat by combined treatment with 2α-methyl-9α-chlorocortisol acetate and phosphates can be inhibited by concurrent treatment with NaCl, KCl, $KHSO_4$, K_2SO_4, CH_3COOK, $MgCl_2$, $CaCl_2$, and NH_4Cl.

This protective effect has not been duplicated either by water deficiency or by administration of excess water; hence, the prophylactic action of the electrolytes cannot be merely a secondary effect of differences in water turnover.

Unlike the electrolytes, large doses of glucose actually aggravate the phosphate-steroid-intoxication syndrome.

The authors are greatly indebted to The Upjohn Company for generously supplying 2α-methyl-9α-chlorocortisol acetate.

REFERENCES

1. Selye, H., Mintzberg, J., and Rowley, E. M.: J. Pharmacol. & Exper. Therap. **85**:42, 1945.
2. Selye, H.: Discussion. Laurentian Hormone Conference, Mont-Tremblant, Sept. 1-6, 1957.
3. Selye, H., and Renaud, S.: Proc. Soc. Exper. Biol. & Med. **96**:512, 1957.
4. Selye, H., and Renaud, S.: Production of Focal Myocardial Lesions by Combined Treatment With 2-Methyl-9α-Chlorocortisol (Me-Cl-COl) and Phosphates, Am. J. Cardiol. (In press.)
5. Selye, H., Renaud, S., and Nádasdi, M.: Nonspecificity of the Mechanism That Elicits Myocardial Necroses in Humorally Conditioned Rats, Endocrinology. (In press.)
6. Selye, H., Renaud, S., and Nádasdi, M.: Ability of Various Steroids to Produce "Infarctoid Cardiopathy" in Rats Conditioned by NaH_2PO_4, J. Pharmacol. & Exper. Therap. (In press.)
7. Selye, H.: Conditioning by Cortisol for the Production of Acute Massive Myocardial Necroses During Neuromuscular Exertion, Circulation Res. (In press.)
8. de Salcedo, I., and Selye, H.: Producao de uma "cardiopatia infarctoide" em varias especies animais, Gaz. méd. portuguesa (In press).
9. de Salcedo, I.: Production de una "cardiopatia infarctoide" en el hamster dorado, Rev. clín. españ. (In press.)
10. Selye, H., and de Salcedo, I.: Infarctoid Cardiopathy Produced by Combined Treatment With Hydrocortisone and NaH_2PO_4 in the Primate, J.A.M.A. (In press.)
11. Selye, H.: Med. Klin., Berlin **25**:167, 1929.
12. Selye, H.: Krankheitsforschung **7**:289, 1928.
13. Selye, H.: Am. Heart J. **55**:1, 1958.
14. Selye, H., and Renaud, S.: Protection by KCl Against the Syndrome of Acute "Infarctoid Cardiopathy" With Nephrocalcinosis, Cardiologia (In press).
15. Follis, R. H., Jr.: Bull. Johns Hopkins Hosp. **71**:235, 1942.
16. Liebow, A. A., McFarland, W. J., and Tennant R.: Yale J. Biol. & Med. **13**:523, 1941.
17. Thomas, R. M., Mylon, E., and Winternitz, M. C.: Yale J. Biol. & Med. **12**:345, 1940.
18. Darrow, D. C., and Miller, H. C.: J. Clin. Invest. **21**:601, 1942.

Respiratory Maneuvers in Converting WPW Syndrome to Normal Conduction and Converting Normal Conduction to a WPW Syndrome

Lawrence E. Lamb, M.D., Randolph Air Force Base, Tex.*

The clinician is often confronted with a case of WPW syndrome and is unable to evaluate S-T segment or T-wave changes or to utilize satisfactorily such electrocardiographic tests as exercise tolerance and hypoxia. Recently it was observed that WPW syndrome could be influenced profoundly by inspiration and expiration. Conversion back and forth between normal and WPW type conduction could be controlled by simple inspiration and expiration. This provides an easy method of evaluating the normal electrical events of the heart despite WPW syndrome in certain instances. The purpose of this report is to present two such cases.

CASE REPORTS

CASE 1.—This 29-year-old pilot was asymptomatic at the time of an annual physical examination. A routine electrocardiogram revealed the presence of the Wolff-Parkinson-White syndrome with short P-R interval and prolonged QRS duration (Fig. 1,*A*). There was no past history of of rheumatic fever, hypertension, kidney disease or cardiac symptomatology. He gave no history of any form of tachycardia.

Physical examination gave evidence only of superior health with no significant cardiac findings.

Laboratory studies included: hemogram, normal; blood urea nitrogen, 14.1 mg. per cent; fasting blood sugar, 103 mg. per cent; urinalysis, normal; total cholesterol, 244.8 mg. per cent; cholesterol esters, 181.6 mg. per cent; uric acid, 2.4 mg. per cent; S_f 0-12, 509 mg. per cent; S_f 12-20, 97 mg. per cent; S_f 20-400, 38 mg. per cent. The atherogenic index was 75. The cholesterol/phospholipid ratio was 0.85.

A chest x-ray demonstrated a normal cardiac shadow and pulmonary vascularity.

Electrocardiographic and vectorcardiographic studies were performed. The initial record demonstrated a typical Wolff-Parkinson-White type electrocardiogram, unchanged from numerous records taken since discovery of the abnormality (Fig. 1,*A*). The distinctive features were the short P-R interval, prolonged QRS duration, and secondary S-T segment and T-wave changes.

In the course of studying the effects of respiratory maneuvers on the electrocardiogram, currently under investigation in this laboratory, it was discovered that the WPW type conduction

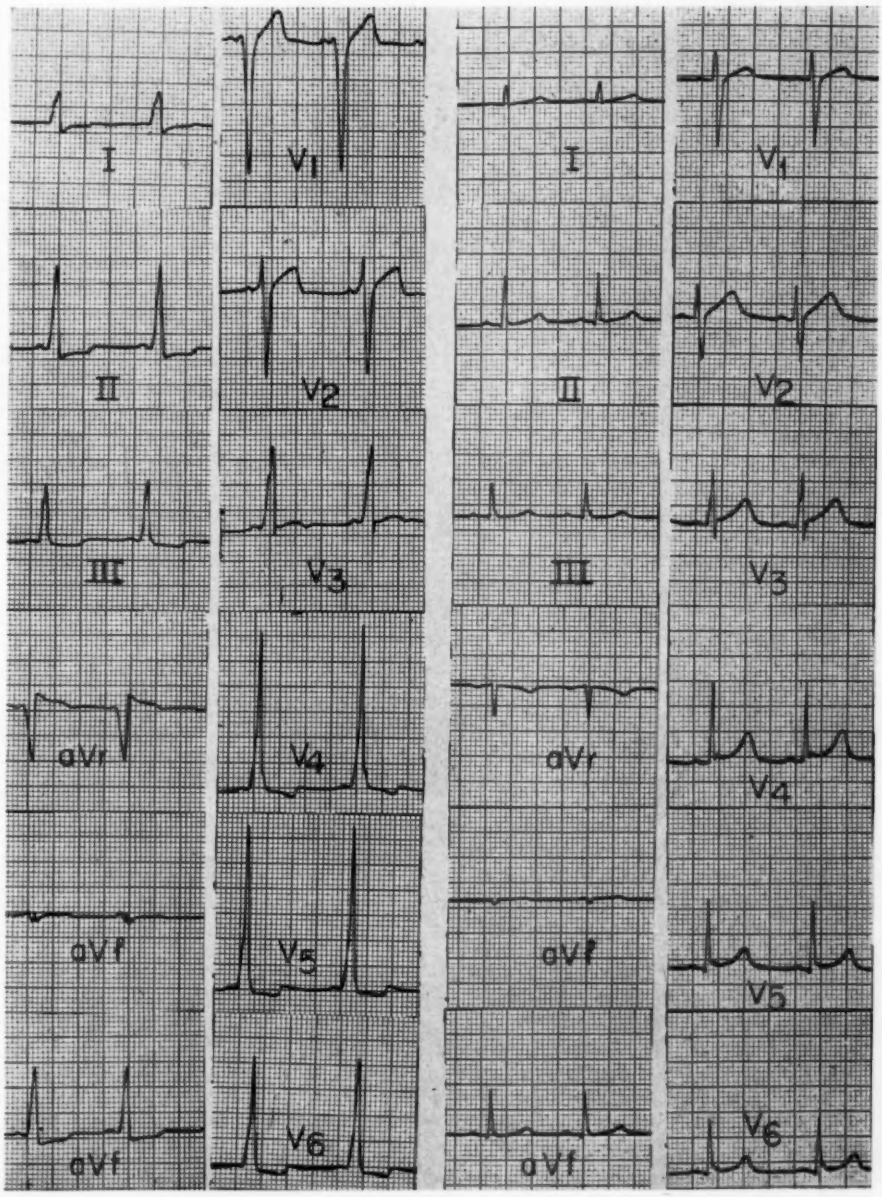
---

From the Department of Internal Medicine, School of Aviation Medicine, USAF, Air University, Randolph Air Force Base, Tex.

Received for publication July 11, 1957.

*Director of Cardiology, and Chief of Internal Medicine.

could be reverted to normal conduction. The patient was instructed to take a deep breath and hold it at the height of inspiration without bearing down. At the point of arrest in full inspiration the tracing reverted immediately to normal conduction (Fig. 2). Expiration was permitted after the breath had been held a short time. Immediately upon expiration the WPW type conduction recurred. The maneuver was successfully repeated at will. In this manner a normal 12-lead electrocardiogram was recorded (Fig. 1,*B*).



A. *B.*

Fig.1.—*A*, This is the usual WPW syndrome tracing seen in Case 1. Note the presence of secondary S-T segment and T-wave changes. Proof of their secondary nature is established by recording a normal ECG (*B*) by holding the breath in deep inspiration. Until the respiratory maneuver was carried out, repeated electrocardiograms demonstrated only a typical WPW syndrome.

Comment.—This case presents several important features. It demonstrates the use of respiratory maneuvers to induce normal conduction in a patient usually presenting a persistent WPW syndrome. The recording of an electrocardiogram with normal conduction points up the fact that S-T segment and T-wave changes in the presence of WPW conduction do not mean underlying cardiac pathology. Because physicians commonly see patients complaining of symptoms, a large number of patients presented to the physician with WPW conduction have recurrent tachycardias. This case is a reminder that not all cases of WPW conduction have recurrent arrhythmias and, in fact, the frequency of arrhythmia in WPW cases for the nonpatient population is not known.

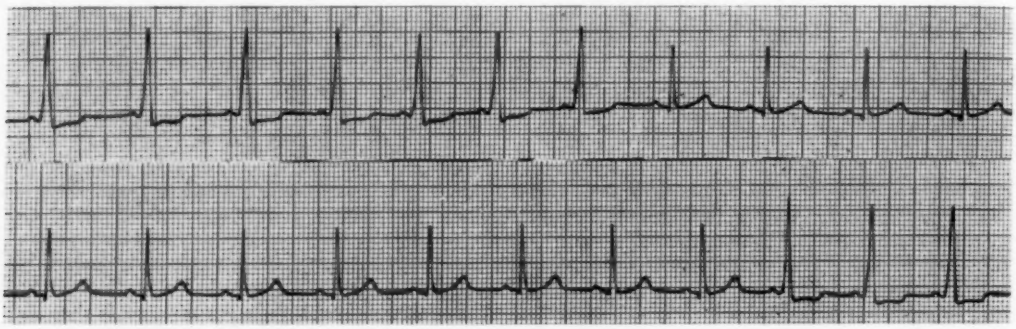


Fig. 2.—This is a continuous strip of Lead II, demonstrating conversion from WPW syndrome to normal conduction. The change occurs at the exact point of holding the breath at the height of deep inspiration; return to WPW occurs at the onset of expiration after breath holding.

CASE 2.—This 36-year-old pilot was asymptomatic at the time of his annual physical examination. An electrocardiogram demonstrated a Wolff-Parkinson-White syndrome. The year prior to this examination an electrocardiogram had been entirely normal. However, it was learned that electrocardiograms recorded 10 years earlier had demonstrated a typical WPW syndrome. The initial electrocardiograms were recorded during hospitalization for a hemorrhoidectomy. The ward physician was recording routine electrocardiograms for a study of normal tracings. The patient gave no history referable to rheumatic fever, hypertension or other symptomatology of underlying heart disease. Prior to adolescence he recalled two occasions of his heart beating fast while attending a movie. There is no other history suggestive of a cardiac arrhythmia.

Physical examination revealed no pertinent findings other than apparent robust health.

Laboratory examinations were as follows: hemogram, normal; urinalysis, normal; fasting blood sugar, 94 mg. per cent; total protein, 6.06 Gm.; albumin, 3.6 Gm.; globulin, 2.4 Gm.; uric acid, 5.0 mg. per cent; total cholesterol, 200 mg. per cent; cholesterol esters, 167 mg. per cent; S_f 0-12, 402 mg. per cent; S_f 12-20, 71 mg. per cent; S_f 20-400, 144 mg. per cent. The atherogenic index was 70. The cholesterol/phospholipid ratio was 0.82.

A chest x-ray demonstrated a normal cardiac shadow with normal pulmonary vascularity.

Electrocardiographic and quantitative spatial vectorcardiographic studies were performed. The method employed in quantitative spatial vectorcardiography is described in detail elsewhere.[1] The initial examination demonstrated a completely normal electrocardiogram and quantitative vectorcardiogram (Fig. 3). By having the subject take a deep breath and hold it, a typical WPW syndrome became evident (Fig. 4). At the onset of inspiration there was intermittent WPW type conduction. While holding the breath in inspiration the WPW syndrome persisted. At the end of expiration the conduction returned to normal. By taking advantage of the influence of respiration, a complete electrocardiogram and quantitative vectorcardiogram showing WPW conduction was recorded (Fig. 5).

A double Master's exercise tolerance test was performed and the intermittent character of the WPW permitted identification of normally conducted complexes before and after exercise. The response to exercise was quite normal. The pilot was taken to a simulated altitude of 45,000 feet in the altitude chamber. An hypoxia demonstration was carried out at 35,000 feet. A continuous electrocardiographic tracing during the chamber flight showed intermittent WPW with no other variations or changes of rhythm.

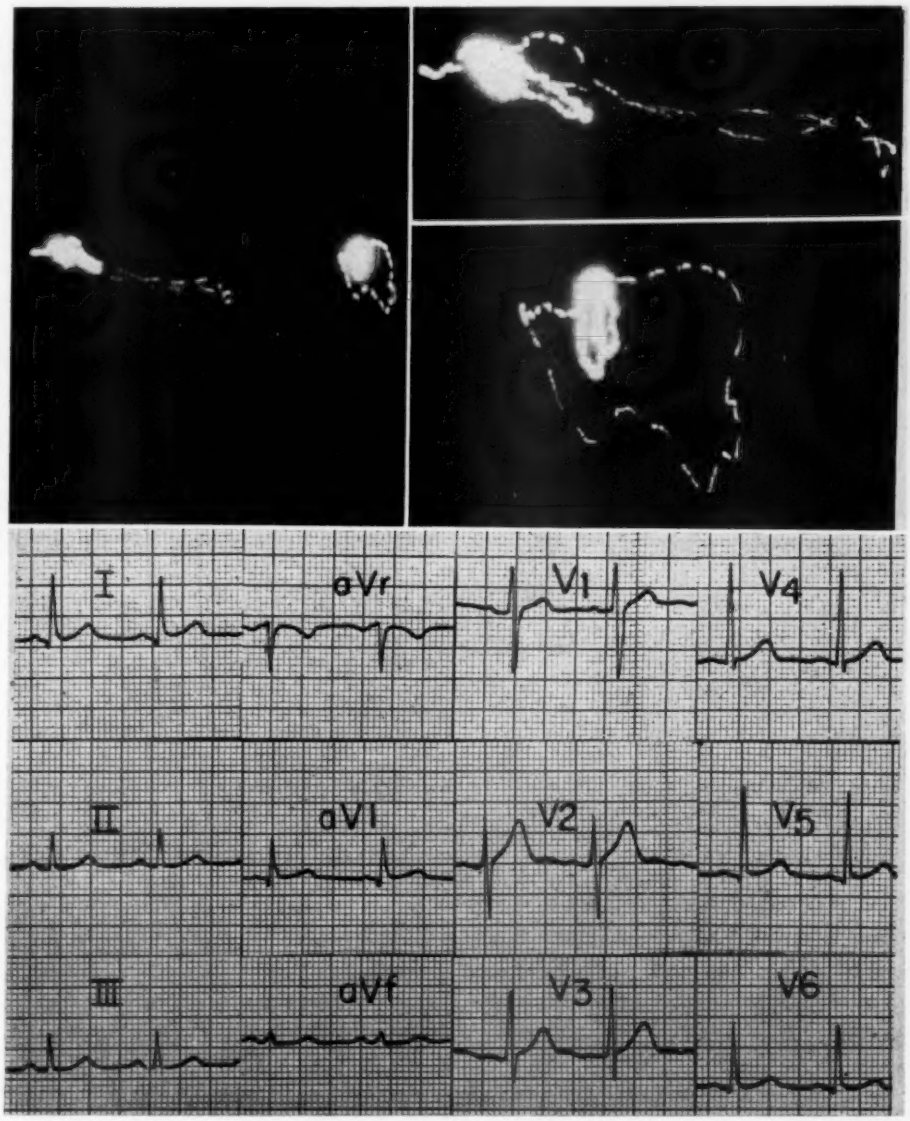


Fig. 3.—This is the quantitative vectorcardiogram and electrocardiogram during normal conduction. Simultaneous frontal and sagittal plane projections are in the upper left-hand corner. A blow-up of the frontal and sagittal projections are in the upper right-hand corner. In the blown-up projections the same amplifications are not maintained. In the frontal (extreme upper right) the most intense illumination is the P area. The middle-size loop extending more leftward is the T loop, and the large loop is the QRS loop. Note the early rightward course comparable to the early Q wave in Lead I. In the sagittal enlargement (left profile) the P loop is just posterior to the T loop. The qualitative and quantitative features of the VCG are quite normal. The routine 12-lead electrocardiogram is recorded at full standard and is normal.

Comment.—This case demonstrates conversion from normal conduction to WPW type conduction on inspiration, or the opposite circumstance from the first case. The use of respiratory maneuvers permitted evaluation of exercise response by the electrocardiogram. It is interesting that there is no history suggestive of arrhythmia since adolescence and that no evidence of arrhythmia occurred with exercise, altitude exposure or hypoxia.

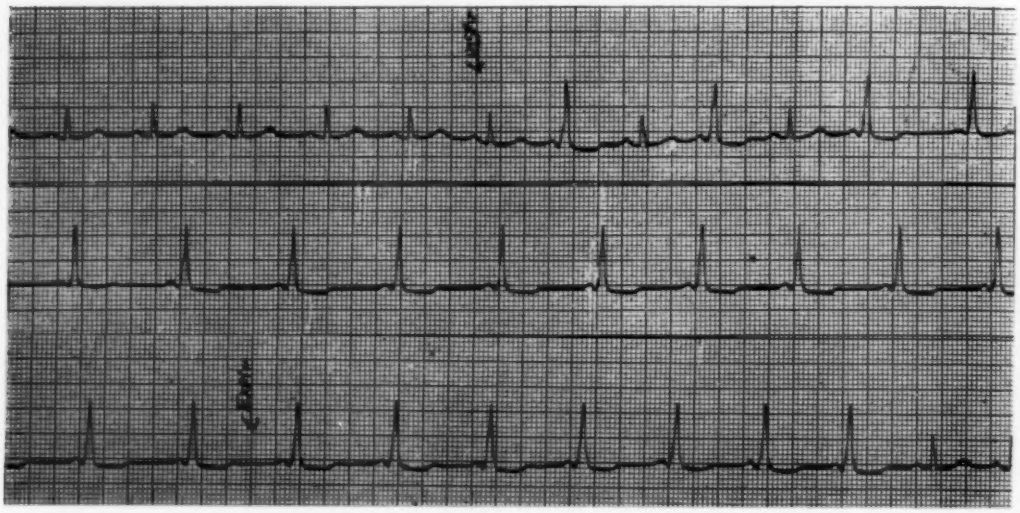


Fig. 4.—This is a continuous strip of Lead II showing the transition from normal conduction to the WPW syndrome on inspiration (Case 2). Note that a few cycles after the onset of inspiration there is an intermittent WPW syndrome. It appears that either normal conduction or WPW conduction occurs without any intermediate type complexes.

DISCUSSION

It is difficult to explain why respiratory maneuvers control changes in WPW conduction. In one case, inspiration induced a change from normal to WPW type conduction. In another instance, inspiration converted WPW conduction to normal conduction. Since holding the breath at the height of inspiration produces marked vagal slowing in normal subjects, it was first thought that vagal inhibition prevented WPW conduction. The second case does not bear out this theory; in fact, little change in rate was noted in either case secondary to respiratory maneuvers.

Knowledge that the WPW syndrome may be converted to normal conduction by respiratory maneuvers provides a means of evaluating normal conduction in certain individuals presenting as the WPW syndrome. In such an instance the T waves and S-T segment variations may be evaluated and even a satisfactory exercise tolerance test performed. While atropine may induce a tachycardia and abolish WPW conduction, its administration precludes a satisfactory exercise tolerance test. Changes in cardiac rate, and visceral pooling after atropine negate many possible studies.

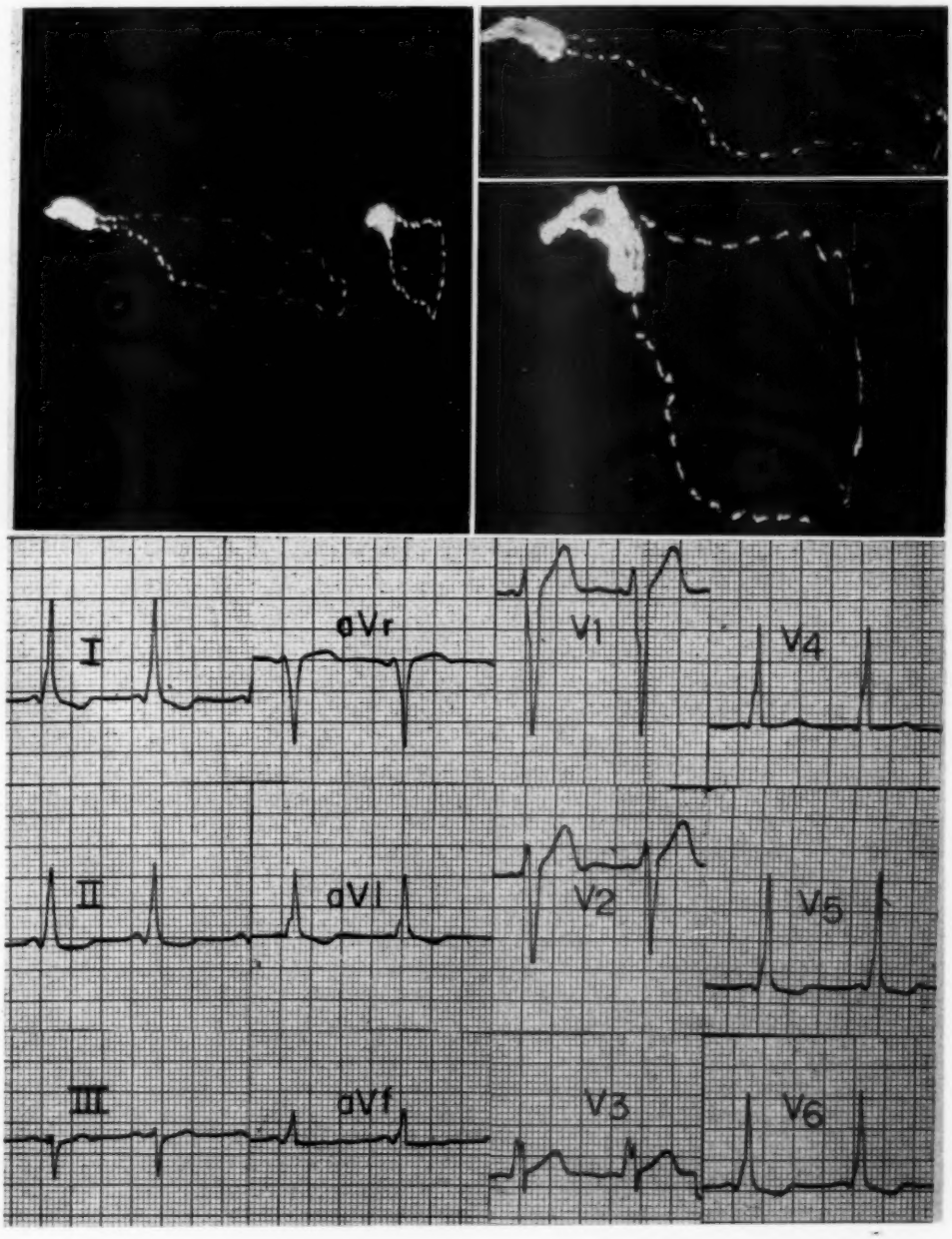


Fig. 5.—This is the quantitative VCG and ECG during WPW type conduction in Case 2. The typical quantitative VCG (frontal and sagittal projections) is depicted in the upper left-hand corner. The blown-up projections of frontal and sagittal views are in the upper right-hand corner. In the enlarged frontal projection the most rightward portion is the T loop. In the sagittal (left profile) view the T loop is the most anterior event. The slow moving initial anterior event of ventricular excitation has a small upward course, sweeps just to the right of the point of origin, and moves downward and leftward. The terminal portion of the QRS loop joins directly into the anterior course of the large T loop. There is a complete change in all phases of ventricular excitation and recovery from normal conduction to WPW conduction.

The second case demonstrates the confusion that may exist when intermittent normal records and WPW conduction is observed at different examinations. This is not infrequently seen in the WPW syndrome.

Both cases point up the absence of arrhythmia in patients with WPW syndrome who are not consulting the physician of their own volition. By evaluating patients on routine examinations the author has been impressed with the relative infrequency of tachycardia in WPW syndrome in a nonpatient population. An analysis of these cases will be presented in a subsequent report.

It should be pointed out that not all examples of WPW syndrome have been converted to intermittent WPW by respiratory maneuvers. The difference between cases with the respiratory phenomenon and those without it remains obscure.

SUMMARY

Two cases are presented which demonstrate the control of intermittent WPW syndrome by respiratory maneuvers. Electrocardiograms and quantitative vectorcardiograms are presented. One case was also studied by exercise tolerance, simulated altitude, and hypoxia.

REFERENCE

1. Lamb, L. E.: Fundamentals of Electrocardiography and Vectorcardiography, Springfield, Ill., 1957, Charles C Thomas.

Alternation of A-V Conduction Time

Richard Langendorf, M.D., Chicago, Ill.

Alternation of A-V conduction time was observed in the experimental animal with normal rhythm and depressed A-V conduction[1] or during rapid stimulation of the atria.[2] In man, the phenomenon was first reported—and its mechanism explained—in a case of auricular flutter with 2:1 A-V conduction[3]; only much later was alternation of the P-R interval observed in patients with normal sinus rhythm and first or second degree A-V block.[4-8] The purpose of this report is to present further clinical observations on alternation of A-V (or V-A) conduction time and to classify the cases according to the underlying mechanism responsible for such alternation.

MATERIAL

Our material consists of 20 cases, 17 of them observed in the Heart Station of Michael Reese Hospital, and 3 recorded elsewhere and made available to us.* The electrocardiograms characterized by alternation of the A-V conduction time were divided into the following three groups: (A) alternation of A-V conduction time in the presence of 1:1 A-V response (7 cases); (B) alternation of A-V conduction time in the presence of 2:1 or 3:1 A-V response (9 cases); and (C) alternation of A-V conduction time associated with the pre-excitation (WPW) syndrome (1 case). Not included were cases of sinus rhythm imitating alternation of A-V conduction as a result of A-V nodal bigeminy or 2:1 A-V block with nodal escapes, because in such cases one of the P-R distances does not represent A-V conduction. Also excluded were instances of simple 2:1 A-V response with constant conduction time, and, for obvious reasons, instances of 3:2 A-V response with the Wenckebach phenomenon. The latter cases are easily recognized as cases of progressive lengthening of A-V conduction with intermittence, when the fundamental rhythm is either a regular sinus or ectopic auricular rhythm (including auricular flutter) which permits identification of the blocked impulse occurring during the longer ventricular cycle. However, in the case of an A-V nodal pacemaker the analogous disturbance of A-V and V-A conduction is more difficult to recognize because the activity of the A-V nodal pacemaker is not reflected in the record regardless of its A-V (V-A) conduction. In order to demonstrate the difficulty arising in distinguishing be-

---

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

This study was aided in part by the Michael Reese Research Foundation.

This article is based on a paper presented at the 28th Annual Meeting of the American Heart Association, New Orleans, La., Oct. 24, 1955.

Received for publication Aug. 29, 1957.

*We are greatly indebted to Dr. D. F. Heiman of Philadelphia, and Dr. A. P. Rusterholtz of St. Paul, for their kind permission to include their observations in our material—Cases A, 7 (Fig. 3) and D, 3 (Fig. 8, *B*, *C*), respectively.

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC DATA OF 17 CASES OF ALTERNATION OF A-V CONDUCTION TIME (GROUPS A-C) AND 3 CASES OF PSEUDO-ALTERNATION OF V-A CONDUCTION TIME (GROUP D)*

GROUP	CASE	FIG.	AGE (YEARS)	SEX	CLINICAL DIAGNOSIS	ATRIAL RATE** PER MINUTE	P-R (F-R)*** IN SEC./100	BASIC DISTURBANCE OF RHYTHM AND MECHANISM OF ALTERNATION OF A-V CONDUCTION
A	1	1	66	F	A.S.H.D.	60	40 and 48	1° A-V block, S. P.
	2		68	M	A.S.H.D.	100	50 and 55	1° A-V block, S. P.
	3	2,*A*	57	F	A.S.H.D.	130	24 and 28	Wenckebach periods, S. P.
	4	2,*B*	35	F	Myocarditis	91	28 and 32	Wenckebach periods, S. P.
	5		60	F	A.S.H.D.	100	48 and 52	Wenckebach periods, S. P.
						77	50 and 54	1° A-V block, S. P.
	6		72	M	A.S.H.D.	136	20 and 24	Wenckebach periods, S. P.
	7	3	68	F	"Palpitation"	72	18 and 28	"Bl." interpol. N.P.S.
B	1		64	F	A.S.H.D.	96	18 and 24	2:1 A-V block, C.C.
	2	4,*A*	53	M	R.H.D., S.B.E.	103	52 and 58	2:1 A-V block, C.C.
	3	4,*B*	62	F	A.S.H.D.	214	12 and 16	A. Flutter, 2:1, C.C.
	4		68	M	A.S.H.D.	300	12 and 15	A. Flutter, 2:1, C.C.
	5		53	M	A.S.H.D.	334	11 and 14	A. Flutter, 2:1, C.C.
	6		60	F	R.H.D.	250	30 and 34	A. Flutter, 2:1, C.C.
	7		61	M	A.S.H.D.	272	16 and 20	A. Flutter, 2:1, C.C.
	8		51	M	R.H.D., Sarcoidosis	200	14 and 18	A. Tach., 2:1, C.C.
	9	5	69	M	A.S.H.D.	214	16 and 20	A. Flutter, 3:1, C.C.
C	1	6	50	M	A.S.H.D.	83	9 and 13	WPW
D	1	7	55	M	Syph. H.D.	214	11 and 14	N. Tach., 3:2 block
	2	8,*A*	76	F	A.S.H.D.	58	20 and 28	N.R., concealed re-entry
	3	8,*B*,*C*	82	F	A.S.H.D.	36	(44), 62	N.R., N.P.S. with forward bl.

*The following 5 cases were described previously by L. N. Katz and A. Pick[8]: A, 2 (Fig. 317); A, 6 (Fig. 189); B, 1 (Fig. 343); B, 3 (Fig. 234); and C, 1 (Fig. 403). We are indebted to the authors for their permission to include their observations in this report.

**Nodal rate in cases D, 1–D, 3.

***R-P in cases D, 2 and D, 3.

A.S.H.D.—arteriosclerotic heart disease; R.H.D.—rheumatic heart disease; S.B.E.—subacute bacterial endocarditis; S.P.—supernormal phase of conduction; C.C.—concealed conduction; N.P.S.—nodal premature systoles; N. Tach.—nodal tachycardia; N.R.—nodal rhythm.

tween alternation and pseudo-alternation of A-V (V-A) conduction, a group of differential diagnosis (D) was added, consisting of 3 instances of A-V nodal rhythm or A-V nodal tachycardia with apparent alternation of V-A conduction time.

Pertinent clinical and electrocardiographic data of all 20 cases are summarized in Table I, and some of the records are reproduced in Figs. 1-8.

COMMENT

In Group A (1:1 A-V conduction or occasional dropped beats—Figs. 1-3) half of the patients had an auricular rate of 100 or more, and all except one had a prolonged P-R interval. The alternating conduction times differed by about 0.04 to 0.10 second, and the shorter P-R interval in all cases followed the shorter R-P distance. This is in contrast with what is usually found with depressed conductivity in the A-V junction; it suggests the supernormal phase of conduction as the mechanism responsible for the alternation of P-R. It is significant that the phenomenon was observed in some patients who in the same record, or at other times, showed progressive lengthening of P-R with dropped beats (Fig. 2). Fig. 2,*B* at one time shows progressive prolongation of P-R after a dropped beat followed by another dropped beat (Wenckebach phenomenon); at another time, it shows progressive lengthening of P-R followed by sudden shortening

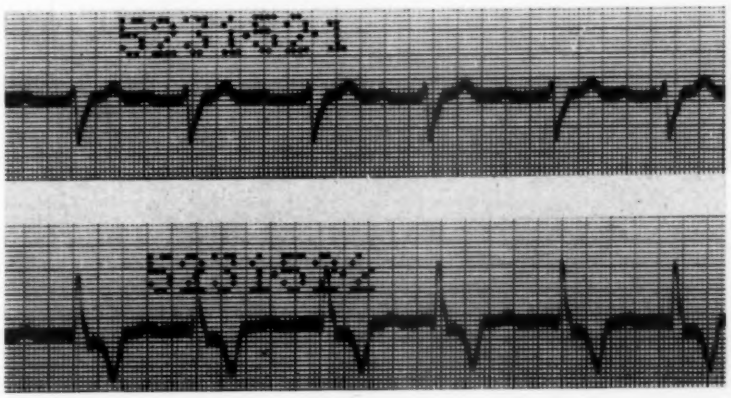


Fig. 1.—Regular sinus rhythm, first degree A-V block with alternation of A-V conduction time and intraventricular block. Note that the shorter P-R intervals follow the shorter R-P distances, suggesting a supernormal phase of conduction. Alternative interpretations, viz., 2:1 A-V block with nodal escapes or first degree A-V block with late nodal premature systoles, appear unlikely in view of preceding and subsequent records.

which initiates alternation of prolonged P-R intervals with the shorter P-R following the shorter R-P. In some records of Case A, 5 (not illustrated) alternation of A-V conduction time was not continuous, yet the shorter R-P distances were associated with the shorter P-R intervals giving rise to occasional shortening of the ventricular cycle. Case A, 7 (Fig. 3), the only one without prolongation of both A-V conduction times, presents a different and most unusual mechanism of alternation of A-V conduction time, confirmed beyond doubt by other records of the same patient,[9] viz., lengthening of P-R as a result of blocked (in both directions) and interpolated A-V nodal premature systoles.[10]

In Group B (2:1 and 3:1 A-V response—Figs. 4, 5) there are 2 cases with sinus rhythm and a sinus rate close to 100, and 7 cases of auricular flutter or ectopic auricular tachycardia with auricular rates from 200 to 334. The alternating P-R intervals in the cases with sinus rhythm differ by 0.04 to 0.06 second, and the corresponding A-V conduction time in the cases of auricular tachycardia

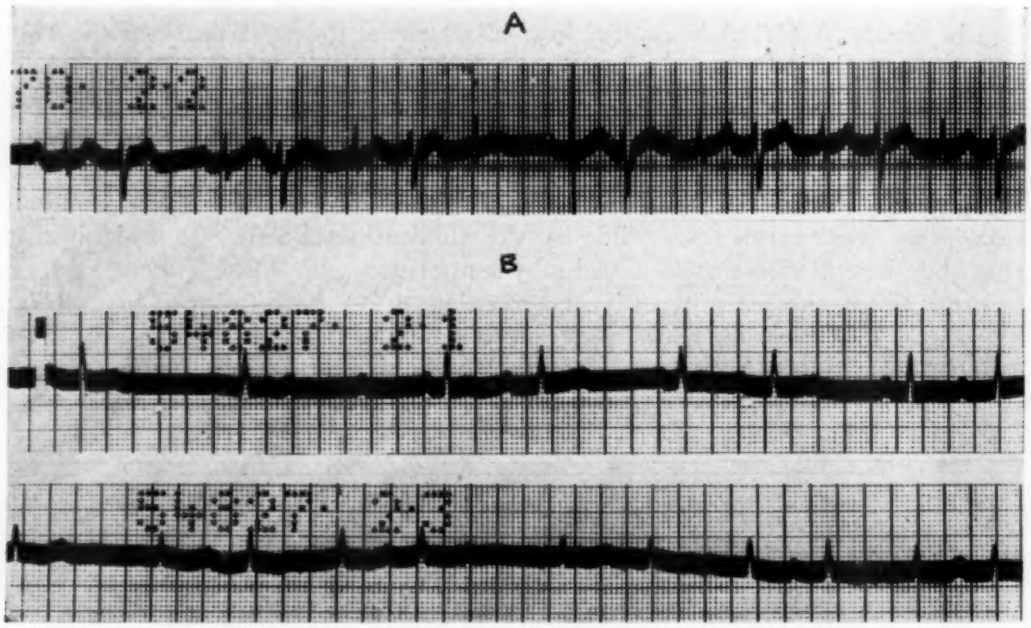


Fig. 2.—*A*, Shows atrial paroxysmal tachycardia with irregular ventricular response. Initial 3:2 A-V response is followed by 6:5 response and then by a long run of 1:1 conduction with alternation of A-V conduction time and varying degrees of aberrant ventricular conduction of the beats with the shorter P-R intervals. That the bizarre beats are conducted and not ectopic premature beats is evident in the first portion of the record, clearly indicating dropped beats after critical shortening of R-P rather than intermittent extrasystolic bigeminy. *B*, Reveals sinus rhythm with shifting pacemaker and second degree A-V block. In the upper tracing, blockage of two consecutive P waves (3:1 A-V block) followed by 3:2 A-V block with the Wenckebach phenomenon; this suggests that the instance of 3:1 block is due to abortive 3:2 conduction (concealed A-V conduction of the second impulse being responsible for blockage of the subsequent [third] impulse). In the lower tracing, instead of the expected 3:2 A-V block, A-V transmission continues with alternation of A-V conduction time, the shorter R-P distances being followed by the shorter P-R intervals (supernormal phase of conduction).

or flutter by 0.03 to 0.04 second. Whenever P-R (F-R) is long, the preceding nonconducted P (F) is seen to occur later in diastole than in the cycles where the nonconducted P (F) precedes a short P-R interval. Case B, 2 (Fig. 4,*A*) demonstrates that such an early impulse may, on occasion, be fully conducted; this suggests strongly that at other times it may be partially conducted ("concealed conduction"[7]) and be responsible for lengthening of the subsequent A-V conduction time. One of the cases (B, 5 which is not illustrated) demonstrated that such alternation of A-V conduction time may be an intermittent phenomenon, and another case (B, 6, also not illustrated) revealed that the alternating P-R intervals may vary in duration. Case B, 9 (Fig. 5) exhibits a similar mechanism in a case of auricular flutter with 3:1 A-V response, a hitherto

undescribed phenomenon as far as we know. As indicated in the diagram, the 3:1 response respresents an abortive attempt at 3:2 conduction[11] and the alternation in ventricular cycle length is explained by the greater extent of penetration of every other first nonconducted impulse; the latter not only prevents conduction of the subsequent impulse (second nonconducted impulse) but influences speed of conduction of the beat following the second nonconducted impulse.

The case representing Group C (pre-excitation [WPW] syndrome—Fig. 6) is clearly an instance of pre-excitation with temporary alternation of P-R as a result of alternation of normal and anomalous A-V excitation. The difference of the two conduction times, which equals the difference in QRS duration, measures 0.04 second.

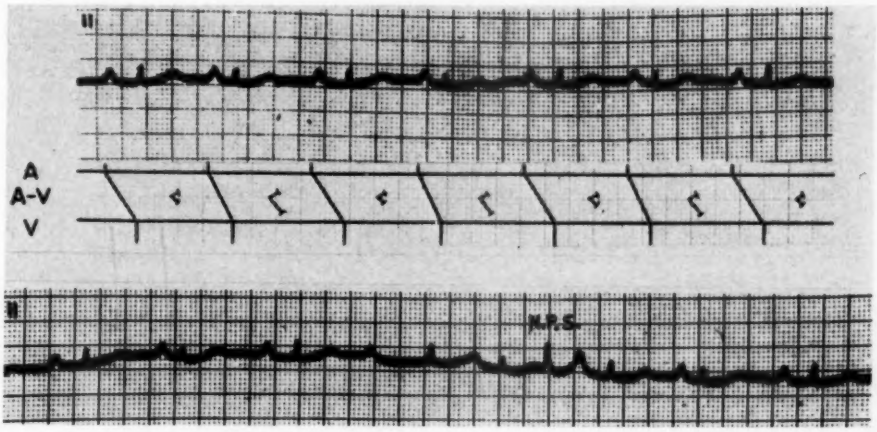


Fig. 3.—Alternation of A-V conduction time due to nonconducted interpolated A-V nodal premature systoles. The upper tracing shows a regular sinus rhythm with alternation of A-V conduction time; the lower tracing shows irregular variations of A-V conduction time and, in the center of the record, an interpolated A-V nodal premature systole (N.P.S.) with prolongation of the postectopic P-R. The latter provides the clue to the interpretation of the varying A-V conduction times: The long P-R intervals are due to the presence of nodal premature systoles which are "blocked" in both directions and interpolated; their partial (concealed) forward conduction is responsible for the delay in conduction of the subsequent sinus impulse. In the upper tracing such blocked interpolated premature systoles can be assumed to occur either only after every second sinus beat or after every beat (continuous blocked nodal bigeminy); the latter assumption is indicated in the diagram since it was substantiated by other records[9] showing continuous bigeminy. The conventions used in the diagram are those used customarily. A-V represents the spread of the impulse through the A-V junction between the atria (A) and the ventricles (V). Blockage of an impulse is indicated by short lines at right angles to the oblique lines, representing the impulse spread; varying length of the oblique lines representing blocked impulses indicates the varying distance which the blocked impulses penetrate into the A-V junction, and varying obliquity varying speed of conduction.

Group D (pseudo-alternation of V-A conduction time—Figs. 7, 8) is illustrated by 3 cases. In Fig. 7, apparent alternation of retrograde conduction time occurs in a regular A-V nodal tachycardia with 3:2 response with the Wenckebach phenomenon of both retrograde and forward conduction. It is of interest to recall that the analogous difficulty of interpretation presents itself for the differentiation between 3:2 S-A block and alternation of S-A conduction time.[12]

Fig. 8,*A* demonstrates alternation of both manifest V-A conduction time and ventricular cycle length in a case of A-V nodal rhythm with reciprocal beating.[13]

As indicated in the diagram, analysis reveals that lengthening of the ventricular cycle in the second half of the tracing is due to abortive (concealed) re-entry after every second A-V nodal beat. Alternation of the R-P interval is due to concealed discharge of the A-V nodal pacemaker by the re-entrant impulse which permits recovery of the fibers responsible for retrograde conduction and prevents the expected intermittence following progressive lengthening of retrograde conduction time. Because of the disturbance in impulse formation of the A-V nodal pacemaker, this case is classified as pseudo-alternation of V-A conduction time.

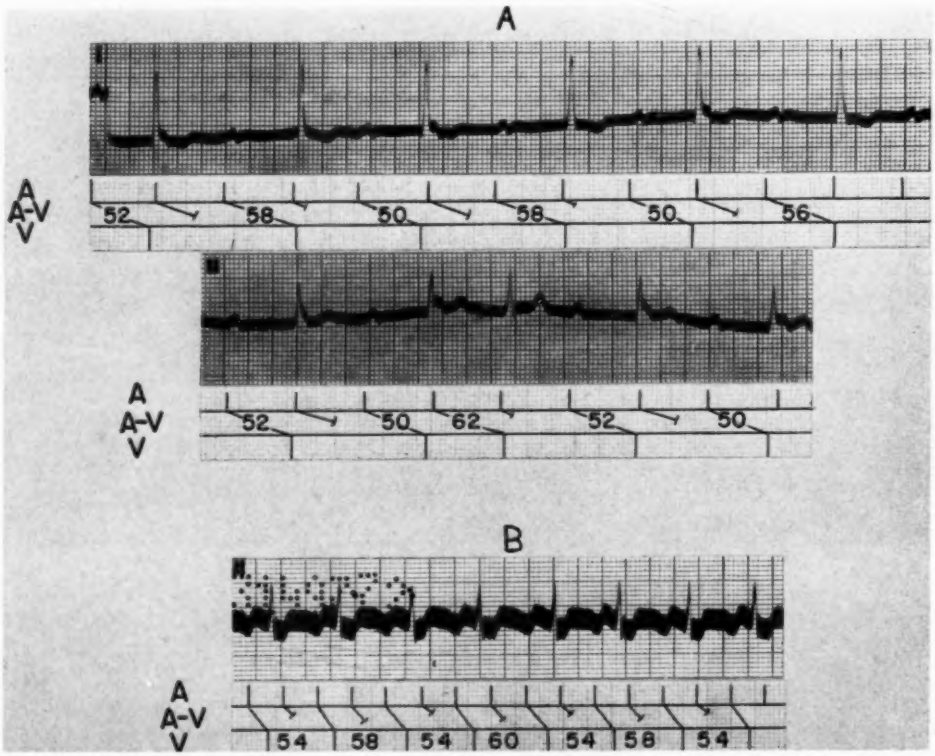


Fig. 4.—Alternation of A-V conduction time due to concealed conduction of alternate "blocked" impulses in (*A*) sinus tachycardia with 2:1 A-V block, and (*B*) atrial flutter with 2:1 response. Note the instance of 3:2 A-V block in the center of the lower tracing of *A*. Diagrams as in Fig. 3; the values in A-V give conduction time; the values in V, the R-R intervals in 1/100ths of a second. Discussed in text.

Finally, Fig. 8, *B*, *C* shows a case of A-V nodal rhythm with prolonged retrograde conduction time. The lower strip of *B* exhibits apparent alternation of V-A conduction time due to ectopic impulse formation. A second record (*C*) taken 4 days later revealed, in Lead II, two A-V nodal pacemakers: a faster one, presumably located in the higher portion of the A-V node (the retrograde P precedes QRS), and a slower one, presumably in the lower portion of the A-V node (the retrograde P follows QRS). In Lead aV_F of the same record all ventricular complexes are preceded by retrograde P waves and the ventricular rate is grossly irregular, due either to A-V nodal premature systoles or—less likely—to a rapid A-V nodal rhythm with second degree block of A-V and V-A conduc-

tion with 3:2 and 2:1 response. The presence of nodal premature systoles in record *C* gives the clue to the interpretation of record *B* as pseudo-alternation of V-A conduction as a result of early A-V nodal premature systoles arising above the dominant A-V nodal pacemaker (and hence conducted to the atria but not to the ventricles) because of interference in the A-V junction between the sites of the dominant and the ectopic pacemakers. The occurrence of the premature impulses after every second dominant beat accounts for apparent alternation of

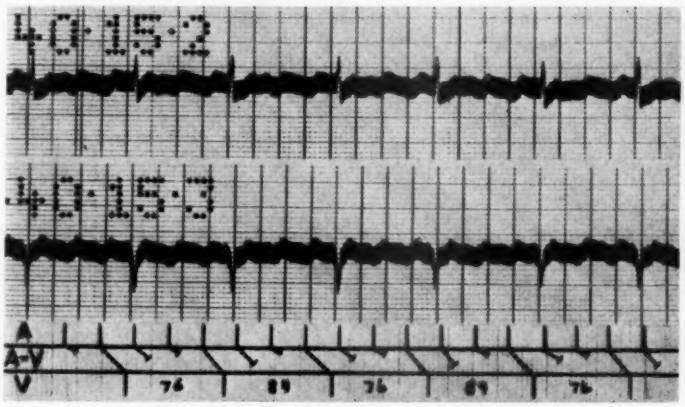


Fig. 5.—Atrial flutter with 3:1 A-V response and alternation of A-V conduction time. Conventions as in Figs. 3 and 4. Discussed in text.

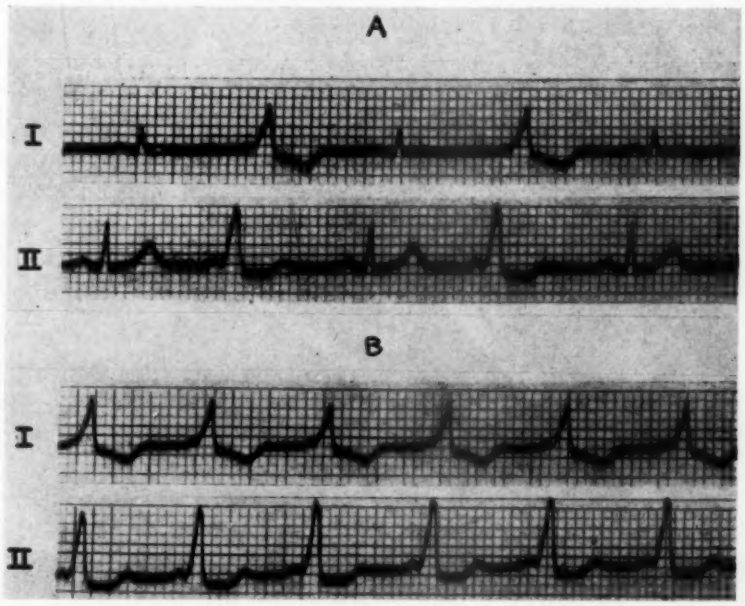


Fig. 6.—A case of pre-excitation (WPW) syndrome. *A*, Shows a regular sinus rhythm with alternation of A-V conduction time due to alternation of normal and anomalous A-V excitation. Bigeminy due to late ventricular premature systoles is ruled out by record *B* showing sinus rhythm with continuous anomalous A-V excitation. From Katz and Pick.[8] Discussed in text.

V-A conduction time of the dominant nodal pacemaker. An alternative interpretation—analogous to the alternative explanation of record *C*—would assume an accelerated dominant nodal rhythm (rate 75) with 2:1 block and concealed retrograde conduction of the alternate "blocked" impulses (cf. Group B). Thus, the distinction is between pseudo-alternation and alternation of V-A conduction time; however, there is no reason to assume a primary form of alternation.

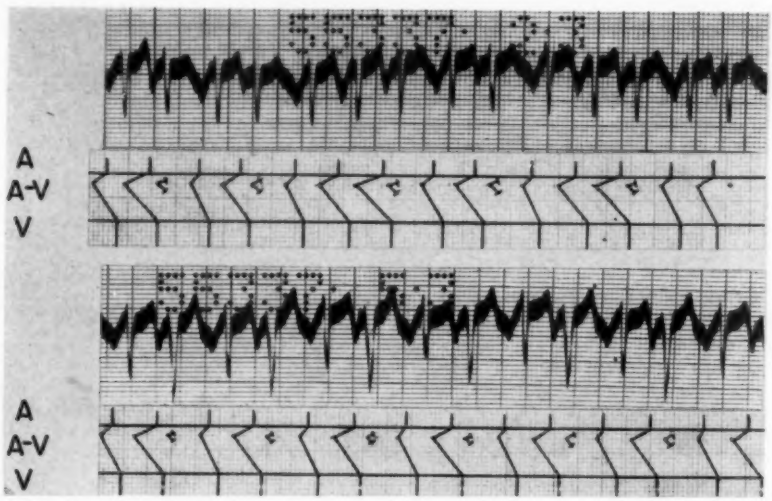


Fig. 7.—A-V nodal paroxysmal tachycardia. The lower tracing shows pseudo-alternation of A-V conduction time, in that a 3:2 A-V and V-A block with Wenckebach phenomenon is present. Note the aberration of every second nodal ventricular complex, explained by lengthening of the refractory period following the slowing of the ventricular rate. Such aberrant ventricular conduction is not present in the upper tracing showing both 3:2 and 4:3 A-V and V-A responses. Conventions as in Fig. 3.

On the basis of the analysis of our material we propose tentatively to reserve the term *alternans* of A-V conduction time for a primary form of alternation, analogous to the phenomenon responsible for the usual manifestation of "electrical alternans"; and to speak of *alternation* of A-V conduction time whenever a mechanism can be demonstrated which is responsible for the lengthening (or shortening) of every other P-R interval. We designate as *pseudo-alternation* of A-V conduction time conditions where: (1) one of the two P-R distances does not represent an A-V conduction time (in the case of a premature beat or escape), or true alternation is not present, insofar as one can determine; (2) a 3:2 response (with a third blocked impulse following the two impulses conducted with varying P-R intervals); or (3) a disturbance in impulse formation of the dominant pacemaker.

Two cases of alternation of A-V conduction time reported by Segers[4-6] are instances of sinus rhythm with 2:1 and 3:1 A-V block. The longer P-R intervals are clearly related to the timing of a preceding "blocked" auricular impulse; thus, in both cases alternation of A-V conduction time can be explained by concealed conduction of blocked impulses, as in the cases of our Group B.

Certain observations have a bearing on our subject although alternation of A-V (V-A) conduction time was not reported in any of them. In a case[14] of second

degree A-V block with P-R intervals of two different categories (0.34±0.02 second and 0.15±0.02 second) a double conducting path in the A-V junction was assumed to be present, although an alternative explanation of the same record given recently[8] appears more likely; it accounts for the longer P-R intervals by concealed conduction of preceding nonconducted impulses, as demonstrated in the cases of Group B of this report. On the other hand, a study of retrograde conduction of ventricular premature systoles[15] revealed two discontinuous orders of magnitude of V-A conduction time in 2 of 15 cases, and the authors postulated that this was due to two separate pathways for retrograde conduction. Similarly, experiments in the dog concerning the transmission of early premature impulses[16] were interpreted as indicative of the existence of a dual A-V transmission system.

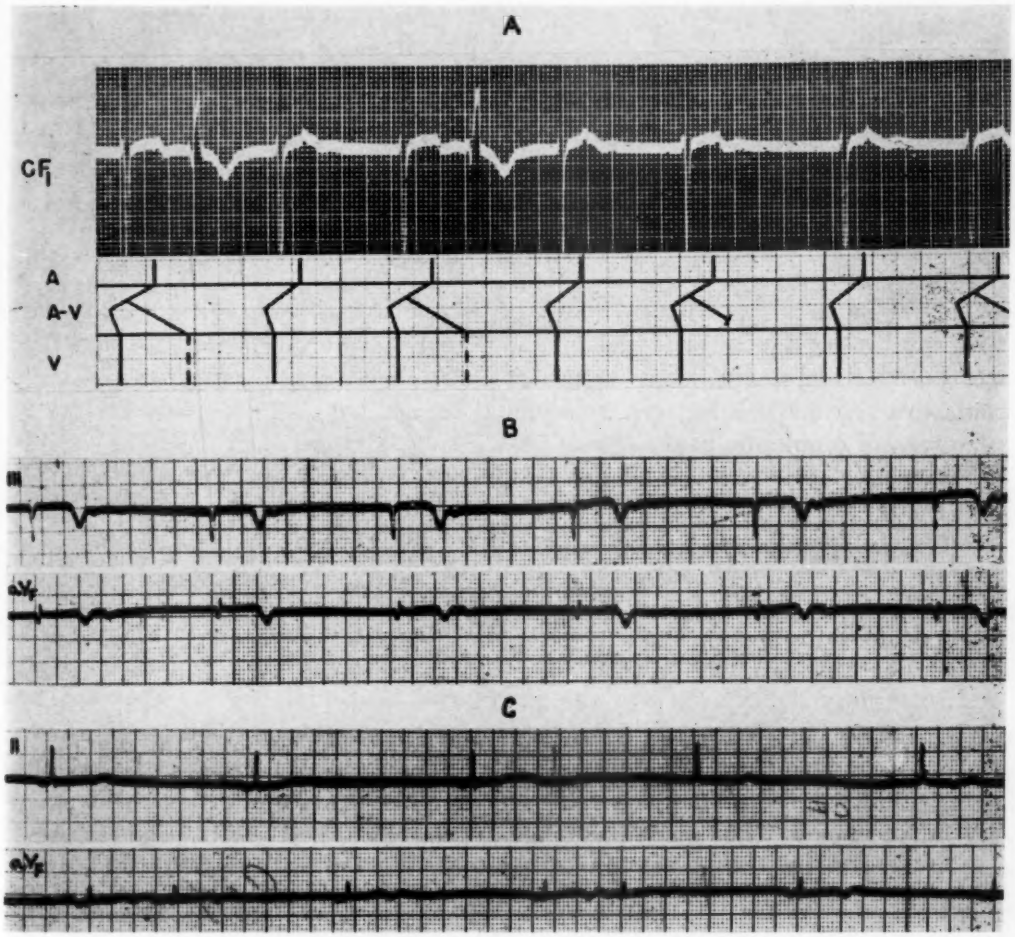


Fig. 8.—*A*, Reveals A-V nodal rhythm with pseudo-alternation of V-A conduction time due to blocked reciprocal beating following every second A-V nodal beat. Conventions as in Fig. 3. Discussed in text. From Langendorf.[7] *B*, Represents A-V nodal rhythm with pseudo-alternation of retrograde conduction time due to nonconducted A-V nodal premature systoles. The upper tracing of *B* shows A-V nodal rhythm with first degree retrograde block (R-P measures 0.54 second); in the lower tracing of *B* every other retrograde P wave occurs earlier and is superimposed on T. It represents a response to an A-V nodal premature systole originating above the dominant pacemaker. Such premature beats with conduction to both atria and ventricles are seen in the lower tracing of *C*. Discussed in text.

It should be emphasized that in the material of this report alternation of A-V (V-A) conduction time can be explained on the basis of well-established physiologic mechanisms without any need to postulate a dual pathway of A-V (V-A) conduction, except in the special case of the pre-excitation syndrome.

SUMMARY

The terms alternans, alternation, and pseudo-alternation of A-V (V-A) conduction time are defined.

Analysis of 17 cases of alternation of A-V conduction time reveals four different mechanisms resulting in such alternation: (1) Supernormal phase of conduction, permitting faster conduction of an auricular impulse occurring early in diastole; this was suggested by all but 1 (viz., 3) of the 7 cases where alternation occurred with 1:1 A-V response. (2) Concealed A-V conduction of "nonconducted" auricular impulses responsible for lengthening of a subsequent P-R (F-R) interval; this could account for alternation in all 9 cases with 2:1 or 3:1 A-V response. (3) Concealed conduction of nonconducted and interpolated A-V nodal premature systoles causing prolongation of the postectopic P-R interval (1 case). (4) Anomalous A-V conduction alternating with normal A-V conduction in cases of the pre-excitation (WPW) syndrome (1 case).

Pseudo-alternation of V-A conduction was demonstrated: (1) in a case of A-V nodal tachycardia with 3:2 block in both directions, (2) in a case of A-V nodal rhythm with reciprocal beating and abortive (concealed) re-entry occurring after every other nodal beat, (3) in a case of A-V nodal rhythm with A-V nodal premature systoles arising above the nodal pacemaker and occurring early after every second dominant beat.

CONCLUSIONS

1. The material of this report permits one to explain alternation of A-V conduction time on the basis of various well-known mechanisms, viz., supernormal phase of conduction, concealed conduction, pre-excitation (WPW) syndrome; it does not reveal any evidence for the existence of a primary alternans of A-V conduction, nor does it warrant the postulation of a dual A-V transmission system except for the cases with the pre-excitation syndrome.

2. Alternation of A-V conduction time occurs in the presence of impaired A-V conduction, regardless of whether this is due to pathologic depression in the A-V junction or to functional (physiologic) interference as a result of an excessive rate of stimulation.

3. The mechanism responsible for alternation of A-V conduction time during 2:1 or 3:1 A-V response, viz., concealed conduction of alternate nonconducted auricular impulses, may be related to that operating during 1:1 A-V response inasmuch as in the former concealed conduction may take place as a result of the supernormal phase of conduction.

4. It would appear that in the human heart alternation of A-V conduction time represents one of the most common manifestations of the supernormal phase of conduction.

5. Alternation of A-V or V-A conduction time has to be differentiated from pseudo-alternation resulting from ectopic impulse formation due to A-V nodal premature systoles or escapes, from 3:2 response in the A-V junction, and from a certain form of A-V nodal rhythm with concealed reciprocal response.

6. Regardless of its mechanism, alternation of A-V conduction time is responsible for an unusual form of bigeminal rhythm.

The author wishes to acknowledge the valuable criticisms of Drs. L. N. Katz and A. Pick.

REFERENCES

1. Lewis, T., and Mathison, G. C.: Heart **2**:47, 1910.
2. Lewis, T., Feil, H. S., and Stroud, W. D.: Heart **7**:247, 1918-20.
3. Kaufmann, R., and Rothberger, C. J.: Ztschr. f. d. ges. exper. Med. **57**:600, 1927.
4. Segers, M.: Acta cardiol. **1**:272, 1946.
5. Segers, M.: Acta cardiol. **6**:289, 1951.
6. Segers, M.: Arch. mal. coeur **44**:525, 1951.
7. Langendorf, R.: Am. Heart J. **35**:542, 1948.
8. Katz, L. N., and Pick, A.: Clinical Electrocardiography, I, Arrhythmias, Philadelphia, 1956, Lea & Febiger.
9. Heiman, D. F.: Pseudo-Atrioventricular Block Due to Non-Conducted Nodal Premature systoles. (In preparation.)
10. Langendorf, R., and Mehlman, J. S.: Am. Heart J. **34**:500, 1947.
11. Langendorf, R., and Pick, A.: Circulation **13**:381, 1956.
12. Clerc, A., Lévy, R., and Calo, A.: Arch. mal. coeur **31**:1175, 1938.
13. Pick, A., and Langendorf, R.: Am. Heart J. **40**:13, 1950.
14. Gertz, G., Kaplan, H. A., Kaplan, L., and Weinstein, W.: Am. Heart J. **16**:225, 1938.
15. Kistin, A. D., and Landowne, M.: Circulation **3**:738, 1951.
16. Moe, G. M., Preston, J. B., and Burlington, H.: Circulation Res. **4**:357, 1956.

A-V Dissociation With Concealed Conduction and Beats With Short P-R Interval and Normal QRS Complex in Association With Hypopotassemic Pattern

L. M. Sanghvi, M.R.C.P. (London), D.T.M. & H. (England), and
S. N. Misra, M.D., Jaipur, India

Cardiac arrhythmias, particularly supraventricular, tend to appear in hypopotassemia.[1] The case of acute gastroenteritis to be reported showed, in association with hypopotassemic pattern in the electrocardiogram, occurrence of A-V dissociation with phenomenon of concealed conduction at one time and beats with short P-R interval and normal QRS complex at another, features which do not appear to have been reported previously.

CASE REPORT

B., a 45-year-old man, was admitted on the morning of March 22, 1957, complaining of hiccoughs and vomiting. On March 17, 2 hours after taking a strong purgative, the patient developed severe diarrhea and vomiting. The diarrhea stopped after 3 days but the vomiting persisted and he started having hiccoughs. He had hardly been able to take anything by mouth since the onset of the illness. He did not have any pain in the chest or dyspnea during the present illness or at any time previously.

On examination, the patient was in great distress with persistent hiccoughs and vomiting and was severely dehydrated. The blood pressure was 120/70 mm. Hg, and the heart rate was approximately 100 per minute, the rhythm being irregular with occasional pauses. Estimation of serum potassium revealed a normal value of 4.5 mEq./L. There was no other significant finding.

The patient was treated with infusions of normal saline intravenously and injections of largactyl (chlorpromazine) intramuscularly. In the evening after admission and again the next morning, 500 c.c. of 1 per cent solution of potassium chloride were injected intravenously and the drug was then given orally 1 Gm. 3 times a day for the next 4 days. He was well on March 27, and was discharged on March 30. He showed no evidence of any cardiovascular disease at the time of discharge and a subsequent Master's test was negative.

Electrocardiograms.—The first electrocardiographic record was obtained soon after admission because of the cardiac irregularity (Fig. 1). It shows depression and sagging of S-T segments and prolonged Q-T interval indicative of a hypopotassemic pattern. Sinus rhythm is indicated by upright P waves with a rate of 97 to 100 per minute. At certain places in the record, the P waves bear no constant relation to the QRS complexes, showing presence of incomplete A-V dissociation. The A-V nodal rate is slightly faster than the sinus rate, being between 100 and 107

From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India.
Received for publication Aug. 29, 1957.

per minute. In all the leads except the first there are ventricular pauses of varying duration while the sinus P waves occur regularly. The arrhythmia can be explained by invoking the concept of concealed conduction. The sinus impulses (marked X) have apparently penetrated beyond the

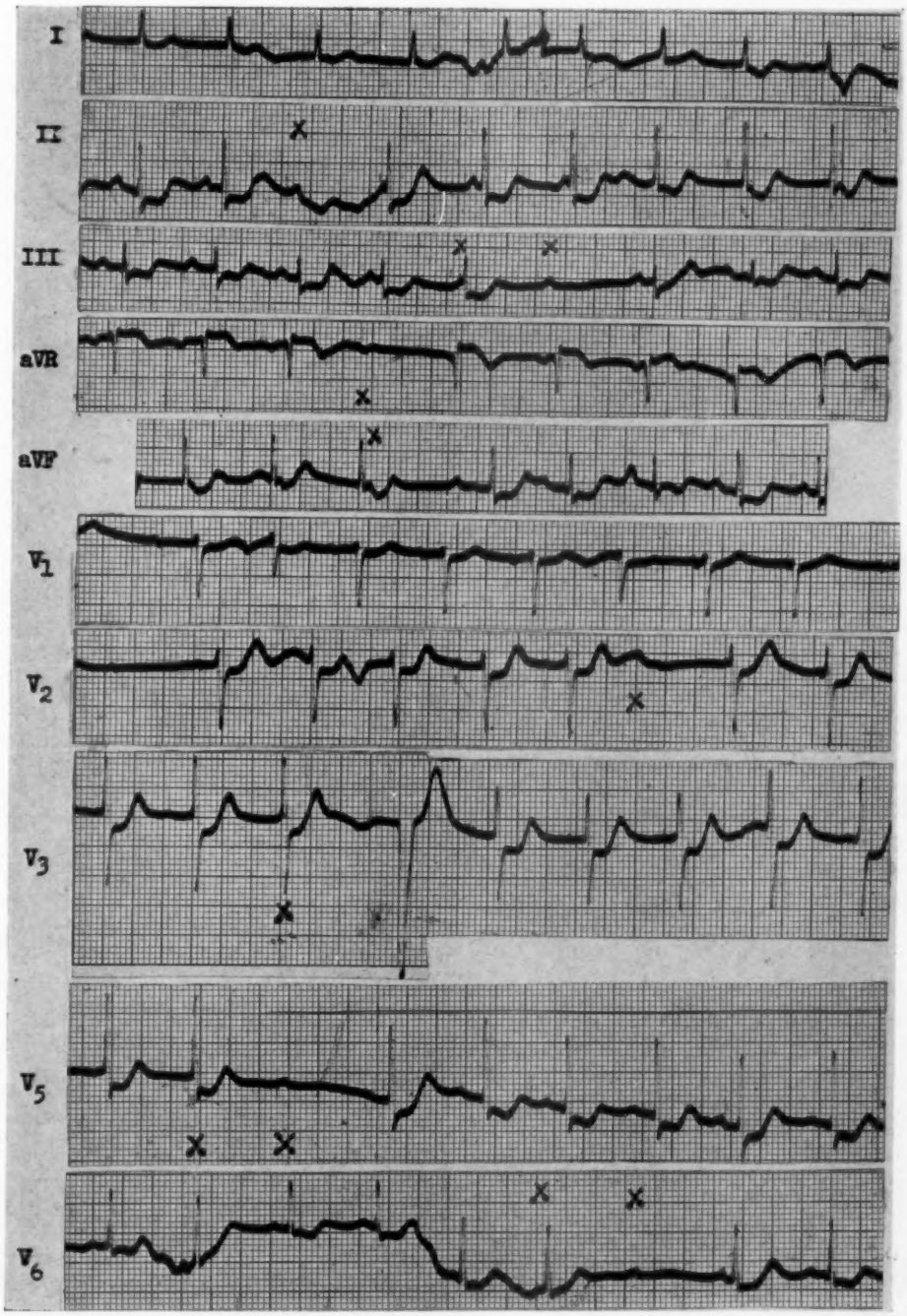


Fig. 1.—Electrocardiogram on the morning of March 22, soon after admission. Depression and sagging of S-T segments indicate a hypopotassemic pattern. Incomplete A-V dissociation with various effects of concealed conduction are described in the text. Artefacts are due to persistent hiccough.

origin of the subsidiary pacemaker in the A-V node, discharging it prematurely, but are prevented from passing on to the ventricles by a second zone of interference in the A-V junction and are, therefore, not followed by QRS complexes. Concealed conduction of these impulses is, therefore, responsible for the pauses. The pauses are terminated either by nodal escapes which initiate A-V dissociation or by conduction of sinus impulses which interfere with the A-V dissociation.

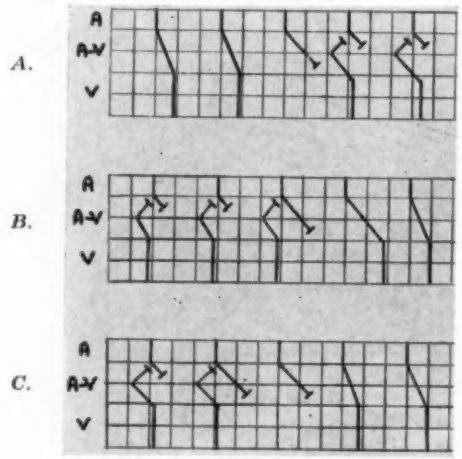


Fig. 2.—A diagrammatic representation of concealed conduction and its effects on subsequent impulse formation and conduction encountered in Fig. 1. A, A-V, and V represent the spread of the impulse between the auricles, A-V junction, and the ventricles, respectively. The short lines at right angles to the oblique lines represent blockage of the impulse and indicate the distance to which it penetrates into the A-V junction. In each strip are represented the ventricular pauses and the beats preceding and succeeding them in various leads (*A*, Leads II, aV_R, V_2; *B*, Leads aV_F, V_1; *C*, Leads III, V_5, V_6). In *A*, the ventricular pause due to concealed conduction is interrupted by escape of the A-V nodal pacemaker which initiates A-V dissociation, while in *B* and *C* it is interrupted by conduction of a sinus impulse to the ventricles, which interrupts the A-V dissociation. In *B*, the next sinus impulse reaches the A-V node when it is partially refractory, and, although conducted to the ventricles, it is delayed with prolongation of the P-R interval. In *C*, there is repetitive concealed conduction of two successive sinus impulses, giving rise to the longest ventricular pauses. On two occasions ($V_{5,6}$) conduction of the third sinus impulse is enhanced with shortening of the P-R interval.

COMMENT

It is seen that when the R-P interval between the blocked sinus P and the preceding R waves of the conducted beat is 0.42 to 0.44 second (II, aV_R, and V_2) a nodal escape beat interrupts the ventricular pause after an R-R interval of 1.12 seconds. When the blocked P immediately follows the nodal QRS, the R-P interval being unmeasurable, the next sinus impulse is conducted after short pauses of 0.80 and 0.90 second. There is, however, either a delayed conduction with prolongation of the P-R interval (aV_F) or an aberrant ventricular conduction (V_3). When the P just precedes the nodal QRS (III, V_5, and V_6), the P-R interval being less than 0.06 second, there is repetitive concealed conduction of two successive sinus impulses, the third sinus impulse being conducted after long ventricular pauses of 1.28 to 1.34 seconds. When the P-R interval is between 0.00 and 0.04 second (V_5 and V_6), the sinus impulse is conducted after a short P-R interval of 0.14 second, but when it is 0.06 second, conduction occurs after a normal P-R interval. The longest as well as the shortest pauses in the record are terminated by conducted beats.

The prolonged P-R interval in Leads aV_F and V_1 does not appear to indicate presence of a first degree heart block because in other normally conducted beats it does not exceed 0.20 second, and a tracing taken after 6 hours, as well as other

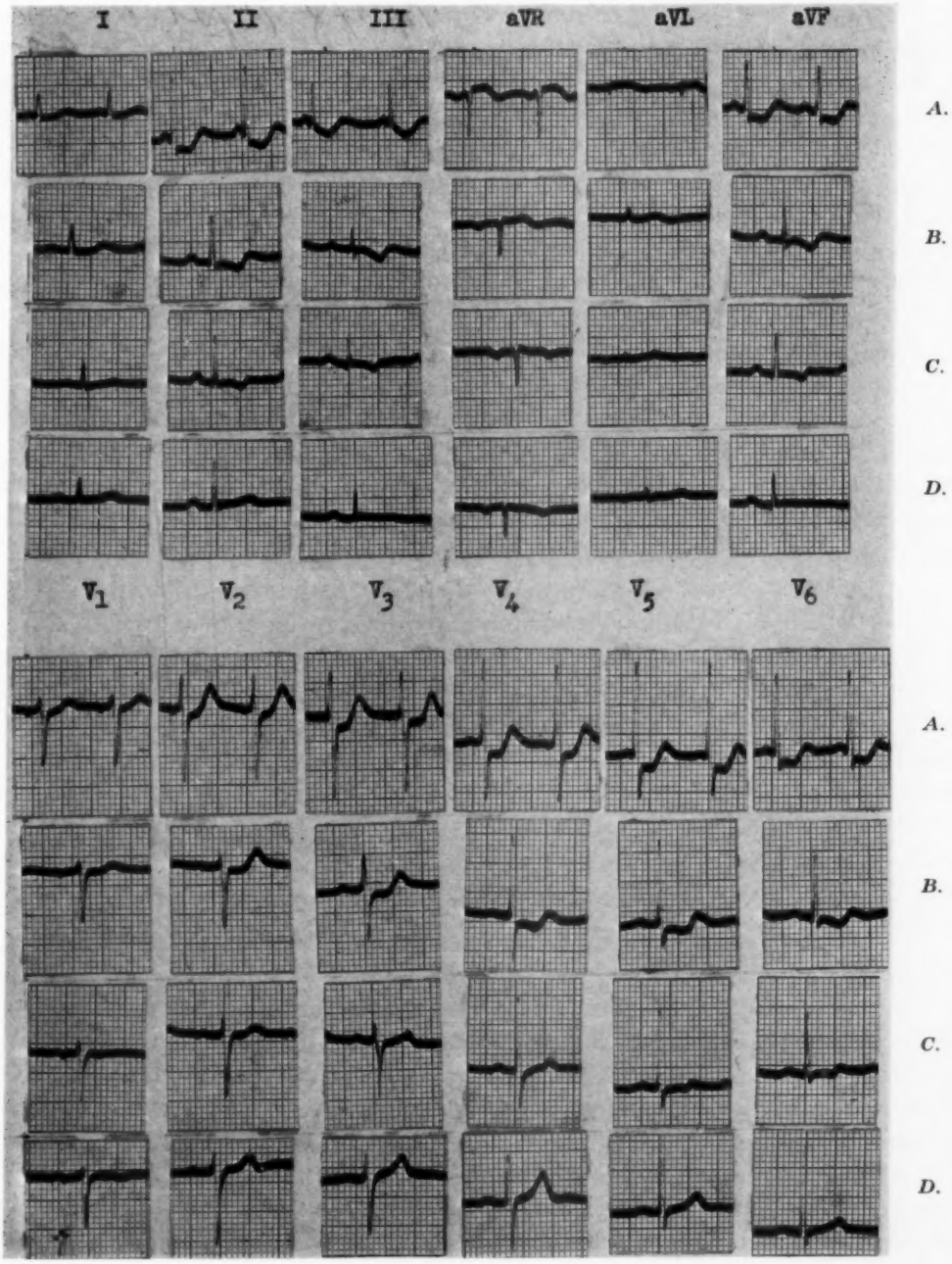


Fig. 3.—*A*, Electrocardiogram taken 6 hours after the tracing in Fig. 1. Regular rhythm with a short P-R interval of 0.11 second and normal QRS complexes. *B*, Electrocardiogram on the morning of March 23. Sinus rhythm with normal P-R interval. *C* and *D*, Electrocardiograms on March 25, and 27, respectively. Gradual regression of the hypopotassemic pattern to a normal record.

subsequent tracings, failed to show the presence of such a block. An interpolated nodal premature beat which is blocked in both directions, and therefore remains invisible, has been reported to prolong the P-R interval of the next beat.[2,3] Such an explanation appears unlikely in the present case because diagnosis of such beats is based on the occurrence in the same record of typical A-V nodal premature systoles and of blocked premature P waves of retrograde contour.[2] It seems, therefore, that concealed conduction has influenced the transmission of the subsequent sinus impulse. This impulse apparently finds the A-V node in a partially refractory state and, although conducted to the ventricles, is delayed, giving rise to a prolonged P-R interval. In Leads V_5 and V_6, however, concealed conduction appears to have enhanced the conduction of the subsequent impulse to the ventricles, the conducted QRS occurring after a P-R interval of only 0.14 second, while the succeeding QRS occurs after a normal interval of 0.18 second.

In brief, concealed conduction of one and, on occasions, two successive sinus impulses (repetitive concealed conduction) produces a disturbance (1) in subsequent impulse formation, shown by a change from normal sinus rhythm to A-V dissociation and vice versa, and (2) in subsequent impulse conduction, shown either by a delay with prolongation of the P-R interval, or by enhancement with shortening of the P-R interval, or by aberrant ventricular conduction. These disturbances are represented diagrammatically in Fig. 2.

A second electrocardiogram taken 6 hours later on the same afternoon, and before the administration of potassium chloride, showed absence of A-V dissociation, and regular rhythm (Fig. 3,*A*). This tracing, however, showed the unexpected occurrence of beats with short P-R interval of 0.11 second and normal QRS complex. This was also transient, since a third tracing taken the next morning showed normal sinus rhythm with a normal P-R interval (Fig. 3,*B*). Subsequent tracings showed regression of the hypopotassemic pattern and a normal record on March 27 (Fig. 3, *C* and *D*).

DISCUSSION

A hypopotassemic pattern in the electrocardiogram occurs after severe vomiting and diarrhea and may be associated with normal serum potassium values.[4] The electrocardiograms of this case, however, revealed other unexpected features hitherto not described. A-V dissociation, seen in the tracing on admission, is rare except after administration of digitalis, quinidine, or Pronestyl, or in acute rheumatic fever and coronary artery disease. There was no such history and no evidence of coronary artery disease in this case. This tracing also illustrated the phenomenon of concealed conduction[5,6] and its aftereffects on the subsequent impulse formation and conduction. The second electrocardiogram showed another unique feature, viz., beats with short P-R interval and normal QRS complex, indicative of a disturbance in conduction in the A-V node.

This case, therefore, illustrates unusual electrocardiographic features apparently caused by some disturbance in the A-V node in association with a hypopotassemic pattern.

SUMMARY

A case of acute gastroenteritis is reported in which hypopotassemic pattern in the electrocardiograms was accompanied by (1) incomplete A-V dissociation and several manifestations of concealed conduction, and (2) beats with short P-R interval and normal QRS complex.

REFERENCES

1. Bellet, S.: A. M. A. Arch. Int. Med. **96**:618, 1955.
2. Langendorf, R., and Mehlman, J. S.: Am. Heart J. **34**:500, 1947.
3. Bix, H. H.: Am. Heart J. **39**:828, 1950.
4. Currens, J. H. and Crawford, J. D.: New England J. Med. **423**:843, 1950.
5. Langendorf, R.: Am. Heart J. **35**:542, 1948.
6. Langendorf, R., and Pick, A.: Circulation **13**:381, 1956.

A Histopathologic Study of the Conduction System in a Case of Complete Heart Block of 42 Years' Duration

Maurice Lev, M.D., Miami Beach, Fla., Julien E. Benjamin, M.D., Cincinnati, Ohio, and Paul D. White, M.D., Boston, Mass.*

INTRODUCTION

In 1952, Benjamin and White[1] presented a clinical report of two patients with long-standing atrioventricular block. The heart of one of these patients has since been subjected to comprehensive histologic study of the conduction system, in addition to that of the entire heart, which forms the basis of the present report. In view of the rarity of comprehensive conduction system studies in congenital[2-13] or acquired[10,14-22] atrioventricular block (9 cases of congenital and about 50 cases of acquired), such a study was deemed important in contributing to electrocardiographic and pathologic interpretation.

BRIEF CLINICAL SUMMARY

This 57-year-old white woman was known to have had a slow pulse since early childhood and complete atrioventricular block proved electrocardiographically at the age of 23 years (Fig. 1). She had never been known to have any serious illness and she had engaged in strenuous nursing activities without any complaints referable to her heart or circulation up to 4 years before death. At this time she felt exhausted and was noted to have an irregular and rapid pulse. An electrocardiogram at this time revealed atrial flutter and high-grade atrioventricular block. The flutter disappeared under digitalis and quinidine therapy, and she remained well until her final illness. Physical examination during this period revealed a heart rate of 32 per minute at the apex, changing little on exercise, with no pulse deficit. A_2 was greater than P_2. There was a Grade 3 rough systolic murmur heard over the entire precordium and transmitted to the interscapular area. The blood pressure was 180 mm. Hg systolic and 65 mm. Hg diastolic. Capillary pulsations were easily demonstrable. A third heart sound was frequently audible. Fluoroscopic examination revealed a dissociated rhythm of the chambers. X-ray examination showed a generally slightly enlarged heart. Electrocardiographic examination at this time revealed complete atrioventricular dissociation (Fig. 2).

On May 10, 1951, the patient experienced a sudden attack of dyspnea while at rest. The dyspnea persisted up to her death. An electrocardiogram revealed atrial flutter with a 7 or 8

From the Research Laboratories of the Mount Sinai Hospital of Greater Miami, Miami Beach, and the Department of Pathology of the University of Miami School of Medicine, Coral Gables, Fla.

This study was supported by a grant from the American Heart Association, and the Heart Association of Greater Miami.

Received for publication July 29, 1957.

*At present, Director, Congenital Heart Disease Research and Training Center, Hektoen Institute, Chicago, Ill.

to 1 heart block, and a ventricular rate of 40 to 50 beats per minute. After quinidine therapy the complete heart block returned and the flutter disappeared. Several hours after the discontinuance of quinidine therapy, the patient had a generalized convulsion, following which she became extremely dyspneic and cyanotic. Five hours later, a syncopal attack occurred during which an electrocardiogram revealed ventricular tachycardia, which vanished when the patient returned to consciousness. Cyanosis and orthopnea persisted until death, which was 36 hours after the onset of her final illness.

POST-MORTEM EXAMINATION

Gross Examination.—Aside from the findings in the heart, the pathologic diagnosis was: (1) chronic passive hyperemia of the lungs and liver, (2) pulmonary edema, and (3) hydrothorax, bilateral.

Heart: The heart weighed 590 grams. The apex was rounded and formed by the left ventricle. From the base, the aorta and pulmonary artery emerged in their normal positions. The right atrial appendage was very large, while the left was minute. The mutual relationship of the various chambers was normal.

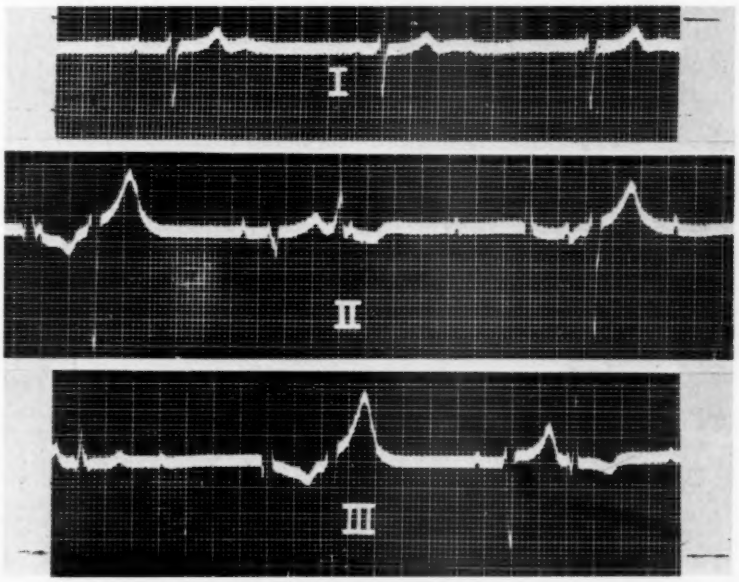


Fig. 1.—Electrocardiogram of Patient L. W., taken in 1916, showing complete atrioventricular block, with atrial rate of 80 to 85 and ventricular rate of 40 per minute (except at the time of ventricular bigeminy).

The right atrium was enlarged and parts of its wall markedly thickened. This was especially true of the atrial appendage, which made up most of the atrium and whose wall and trabeculae were enormously thickened. Likewise, the posterior crest was especially well formed and thickened. On the other hand, the atrial musculature proximal to the sulcus terminalis, and that of the lower part of the anterior and the inferior walls, was rather thin. The superior and the inferior venae cavae entered this chamber in what was considered to be a normal manner. The inferior vena cava was guarded by a prominent eustachian valve which extended from the atrial septum to the anterior wall of the right ventricle, lining the crista terminalis and being anchored at about the tail of the S-A node. The coronary sinus entered this chamber normally, and was guarded by a normal thebesian valve. There was no limbus or fossa ovalis. The endocardium of the sep-

tum at the mouth of the superior vena cava presented an irregular thickening and yellow granular excavations and excrescences. The endocardium marking the outflow region of the coronary sinus was thickened and yellow, but smooth.

The tricuspid orifice measured 11.0 cm. in circumference. Its valve and corresponding chordae tendineae and papillary muscles were normally formed and they presented no pathologic change.

The right ventricle was large and its wall was markedly thickened, measuring 0.5 cm. at the pulmonic orifice, 0.5 cm. at the tricuspid orifice, and 0.2 cm. at the left lateral margin. The sinus of the right ventricle presented a normal configuration. The conus, however, showed an abnormal topography. The septal portion of the crista consisted of three thick bands extending almost horizontally to the left lateral margin. The parietal portion presented a normal architecture.

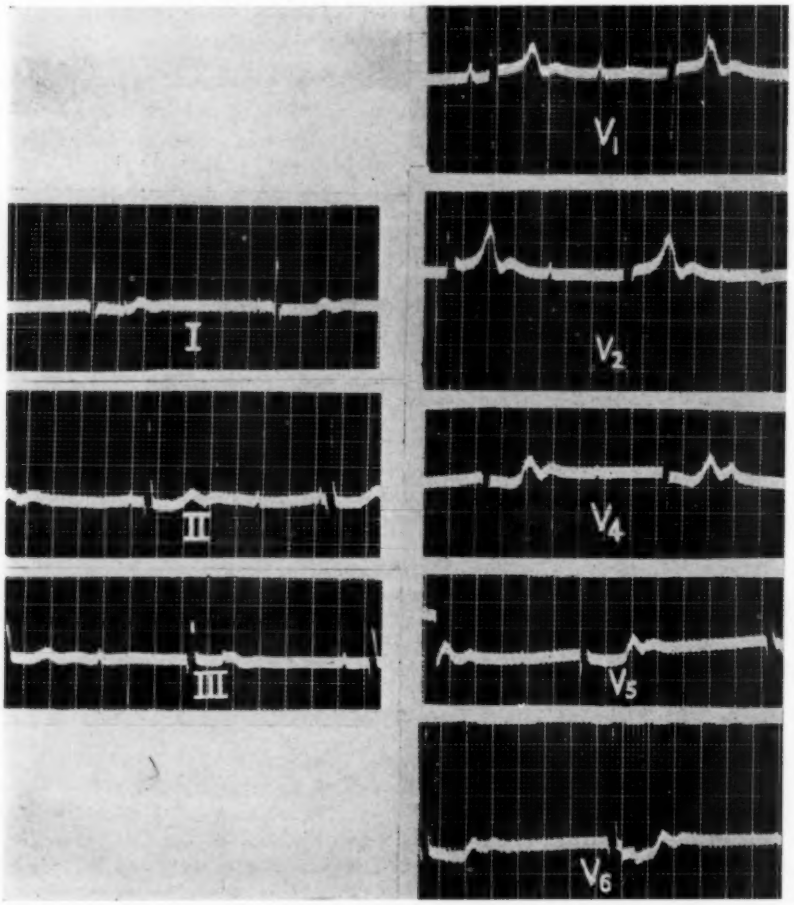


Fig. 2.—Electrocardiogram of Patient L. W., taken Sept. 20, 1950, showing complete atrioventricular dissociation, with atrial rate of 60 and ventricular rate of 30 per minute. The atrial beats came at irregular intervals, whereas the ventricular beats came at regular intervals.

From this chamber emerged the pulmonary artery. Its valve was normally formed and its orifice measured 8.0 cm. in circumference. The base of the pulmonary artery presented marked sclerotic changes. The wall of the pulmonary artery was markedly thickened.

The left atrium was enlarged and its wall was markedly thickened. It received the four pulmonary veins in a normal fashion. The left atrial appendage was seen to be a small nubbin, 1.5 cm. deep, guarded by an opening 1.0 cm. in diameter. The entire endocardium of the left atrium was markedly thickened and geographic. An irregular brown area of parchment consis-

tency, measuring 3.5 cm. in greatest dimension, was present adjacent to the atrial appendage, and above the region normally occupied by the left aspect of the limbus and the fossa ovalis.

The mitral orifice measured 9.5 cm. in circumference. The leaflets, corresponding chordae tendineae and papillary muscles of the mitral valve were normally formed. Its leaflets, however, were somewhat thickened. The left ventricular chamber was large and its wall measured 1.2 cm. in greatest thickness and 0.3 cm. at the apex. The left aspect of the ventricular septum presented a normal configuration. The pars membranacea consisted mostly of an atrioventricular portion.

The aortic orifice measured 7.0 cm. in circumference and its valve was normally formed. The cusps showed minimal sclerotic change. The proximal portion of the ascending aorta showed marked sclerotic change. The ostia and lumina of the coronary arteries were unrestricted. The lining of the coronary arteries showed no change. The left coronary artery was small and terminated as the ramus anterior ventriculi sinistri. The right coronary artery was large, forming the ramus obtusi.

Microscopic Examination.—

Methods: Both atria (excluding the septum) were completely divided into 11 blocks as follows: Block 1 contained the S-A node and the adjacent right atrial and superior vena caval tissue. Block 2 contained the summit of the atrial appendage. Block 3 contained the roof of the left atrium in the region of the right pulmonary veins. Block 4 contained the superior walls of both atria from the atrioventricular junction to the S-A node region and the right pulmonary vein region. Blocks 5 and 6 consisted of the anterior wall of the right atrium from the atrioventricular junction up to Blocks 1 and 2. Block 7 consisted of the proximal part of the anterior wall of the right atrium in the region of the inferior vena cava. Blocks 8 and 9 consisted of the proximal part of the lateral and inferior walls of the left atrium, and Blocks 10 and 11 the distal part adjacent to the atrioventricular junction.

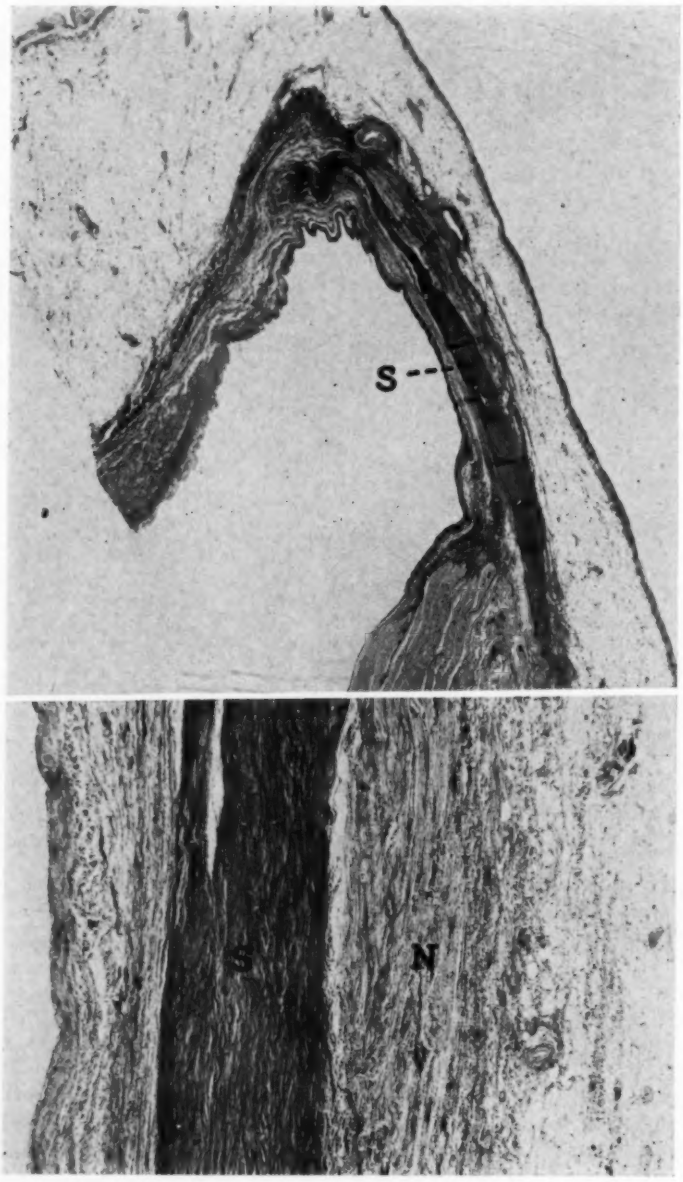
Fig. 3.—S-A node, showing fibrosis formation. S = scar.
(Weigert-van Gieson stain. ×48. Reduced by ¼.)

The atrial and the proximal two thirds of the ventricular septum through the attachment of the moderator band were then fashioned into blocks as follows: Block 12 consisted of the most proximal portion of the atrial septum and the adjoining left atrial wall. Block 13 consisted of the atrial septum in the region where the fossa ovalis should have been. Block 14 included the A-V node and its approaches, and the beginning of the bundle of His. Block 15 included the remainder of the bundle of His, the right and left bundle branches up to the region of the muscle of Lancisi. Block 16 included the remainder of the right and left bundle branches up to the moderator band,

The remainder of the ventricular septum and the anterior and posterior walls of both ventricles were then sectioned as follows: ventricular septum—8 blocks; anterior wall, left ventricle—15 blocks; posterior wall, left ventricle—9 blocks; anterior wall, right ventricle—6 blocks; posterior wall, right ventricle—7 blocks.

Blocks numbered 1, 2, 14, 15, and 16, which contained the S-A node and its approaches, the A-V node and its approaches, the A-V bundle and bundle branches up to and including the proximal portion of the moderator band, were sectioned serially at 8 microns and all sections were retained and were alternately stained with hematoxylin-eosin and Weigert-van Gieson stains.

A.



B.

Fig. 4.—Region of the linea terminalis showing scar adjacent to S-A node. N = node; S = scar. (Weigert-van Gieson stain. *A*, ×7; *B*, ×48. Reduced ¼.)

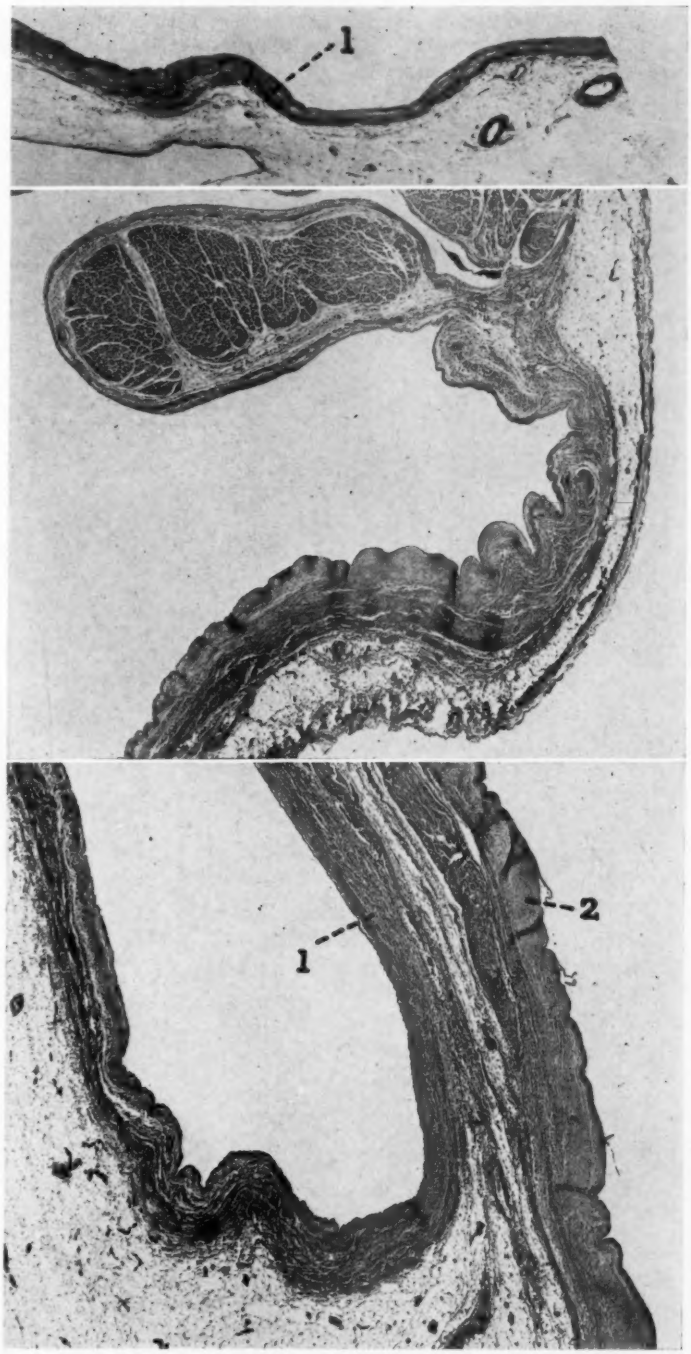


Fig. 5.—Right atrium (hematoxylin-eosin stain). *A*, Superior wall (×5.5). *B*, Anterior wall, distally (×14). *C*, Reflection of the inferior walls of both atria upon the septum in its mid-portion (×16). Note the absence of striated muscle in the superior and inferior walls, and the marked diminution on the anterior wall distally below the appendage. *1*, Thickened endocardium of the right atrium. *2*, Thickened endocardium of left atrium. (Reduced ¼.)

Blocks 3 to 13, which included all the free walls of the atria and the proximal part of the atrial septum, were serially sectioned at 8 microns and every eightieth section was retained. Two sections each were taken from each block of the distal ventricular septum and the free walls of the ventricles and were stained with hematoxylin-eosin and Weigert-van Gieson stains. Thus a

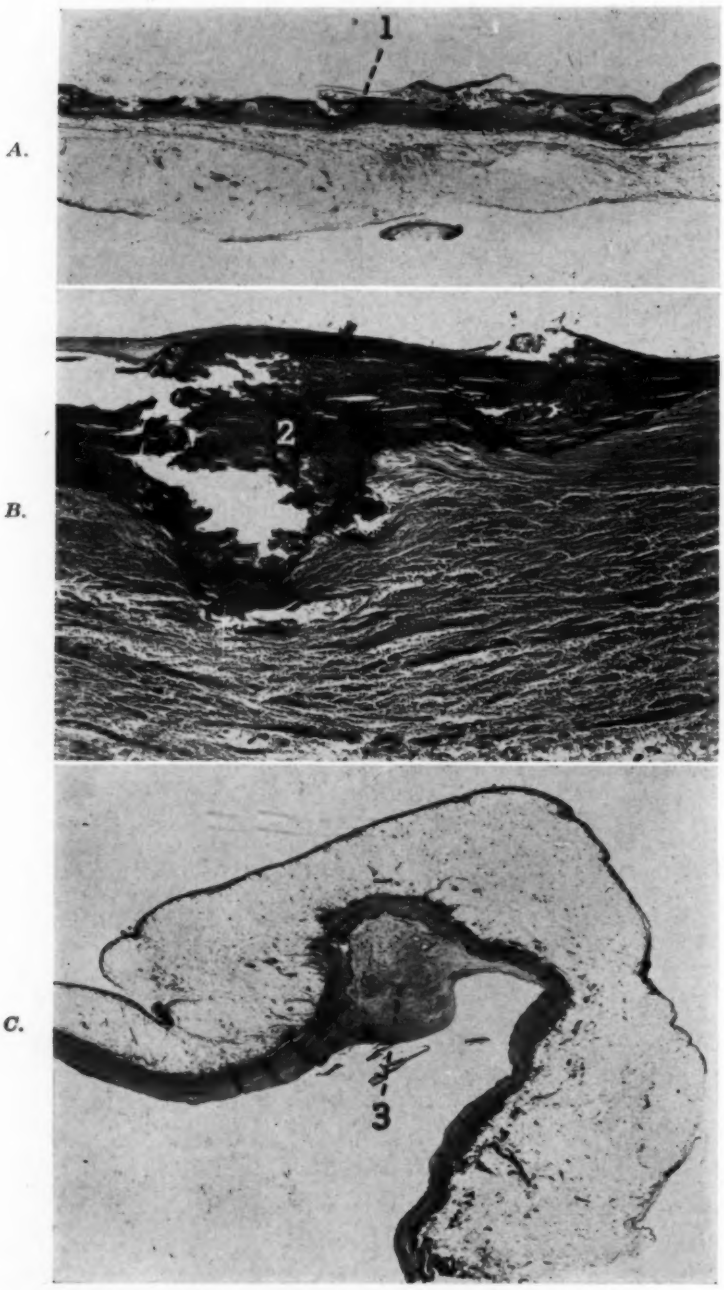


Fig. 6.—Left atrium (hematoxylin-eosin stain). *A*, Superior wall (×5.5). *B*, Superior wall (×45). *C*, Atrial appendage (×6). Note the absence of striated muscle in the superior wall and the atrial appendage, and the endocardial hypertrophy, sclerosis and calcification. *1*, Endocardium. *2*, Calcified zones. *3*, Organized thrombus. (Reduced ¼.)

total of 14,555 sections were cut throughout the entire heart. During the serial sectioning, 60 sections were lost. The gaps thus left were either of no or of minor importance, with the exception of the region of the distal part of the anterior radiation of the left bundle branch, where unfortunate gaps were present.

Histopathologic Findings.—

S-A node and its approaches: The S-A node presented areas of replacement by collagenous connective tissue in which were occasionally interspersed mononuclear cells (Fig. 3). In the region of the linea terminalis, there was a large thick scar which interdigitated with nodal tissue and was also continuous with scar tissue in the posterior crest (Fig. 4). This scar was seen to be continuous with the attachment of the eustachian valve. The atrial tissue adjacent to the S-A node and in the adjacent atrial appendage was punctuated by old scars in addition to occasional zones of late organizing connective tissue. The endocardium in this region showed hypertrophy and sclerosis with vascularization. Occasional hyaline thrombi were noted in a large and small arteriole.

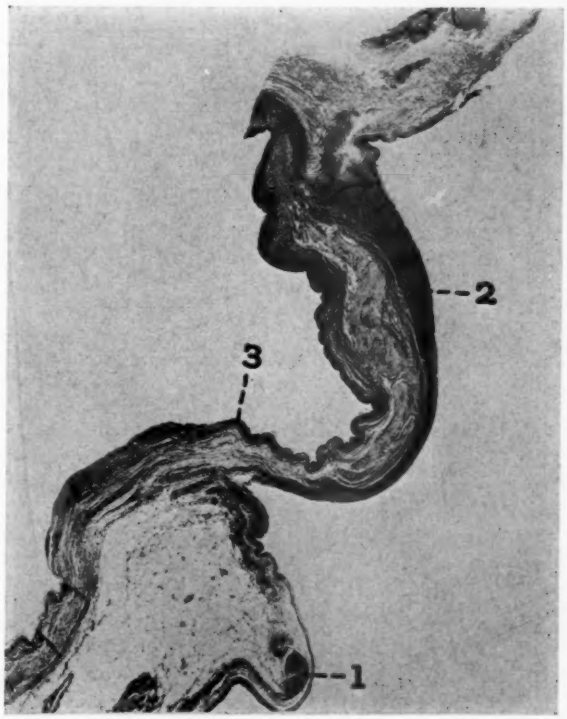


Fig. 7.—Atrial septum in the region of the insertion of the eustachian valve (Weigert-van Gieson stain. ×8). Note almost complete absence of striated muscle. *1*, Insertion of eustachian valve. *2*, Thickened endocardium of right atrium. *3*, Thickened endocardium of left atrium. (Reduced ¼.)

Free walls of the right atrium: The entire inferior portion of the anterior wall, the entire proximal portion of the anterior wall adjacent to the septum, the entire posterior wall, and the most distal part of the roof were almost devoid of muscle (Fig. 5). The wall here consisted of tremendously hypertrophied endocardium, especially with smooth muscle hypertrophy and with marked sclerotic changes and with zones of calcification. Fat tissue lay between the endocardium and pericardium. Wenckebach's and Bachmann's bundles were not present. Thus, the only musculature present in the free wall was in the greatly hypertrophied atrial appendage which formed the only muscular connection with the atrial septum from the right atrium, and was reflected onto it superiorly.

Free walls of the left atrium: The distal portion of the roof of the left atrium was devoid of striated muscle, being replaced by scar tissue with marked calcification (Fig. 6, *A* and *B*). The

endocardium here showed tremendous hypertrophy with marked sclerosis and calcification. This was continued on into the shrunken left atrial appendage in which no striated muscle was present (Fig. 6, *C*), it being completely replaced by scar tissue accompanied by marked endocardial hypertrophy and by an old recanalized thrombus. Likewise the entire distal part of the free walls of

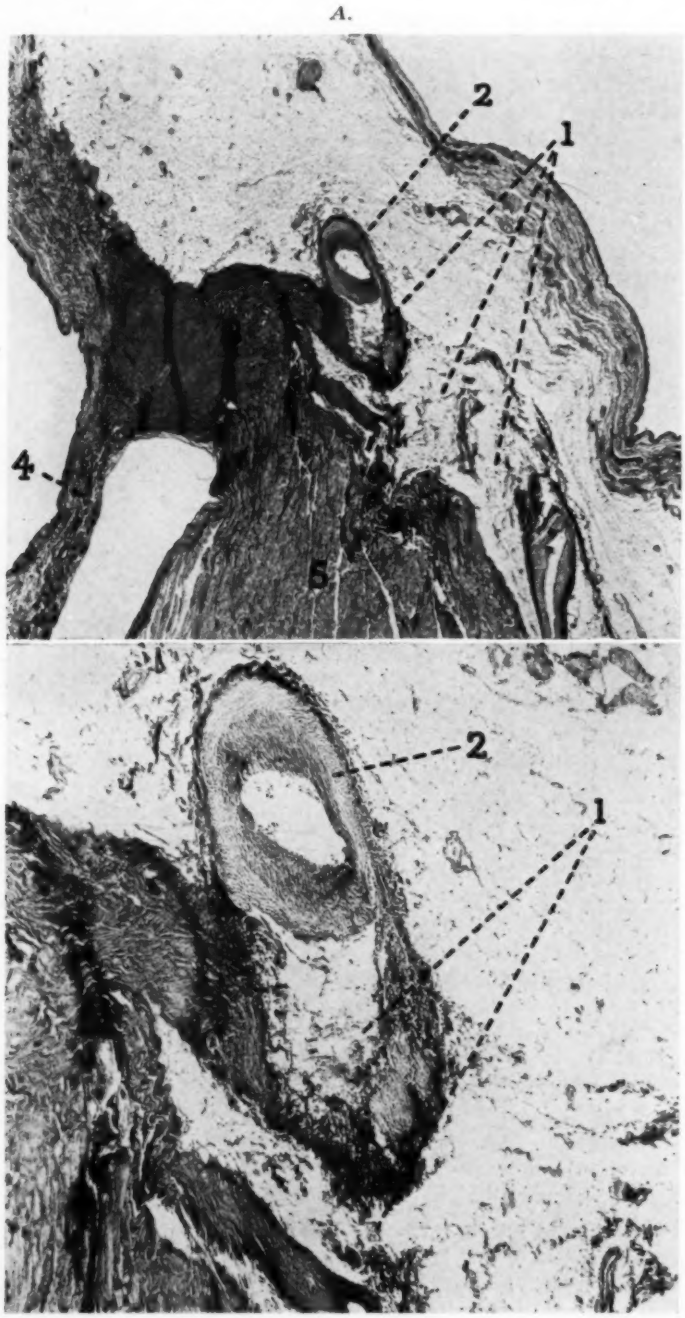


Fig. 8.—Region of the A-V node (Weigert-van Gieson stain. *A*, ×15; *B*, ×48). Note the absence of node. *1*, Region of A-V node. *2*, Branch of ramus septi fibrosi. *3*, Central fibrous body. *4*, Mitral valve. *5*, Ventricular musculature. (Reduced ¼.)

the left atrium was devoid of striated muscle, replaced by fibrous tissue and accompanied by tremendous endocardial hypertrophy. The proximal part of the free walls of the left atrium presented markedly hypertrophied striated muscle with fibrotic patches. This muscle was reflected on to the septum superiorly. The ramus ostii cavae superioris showed no sclerosis.

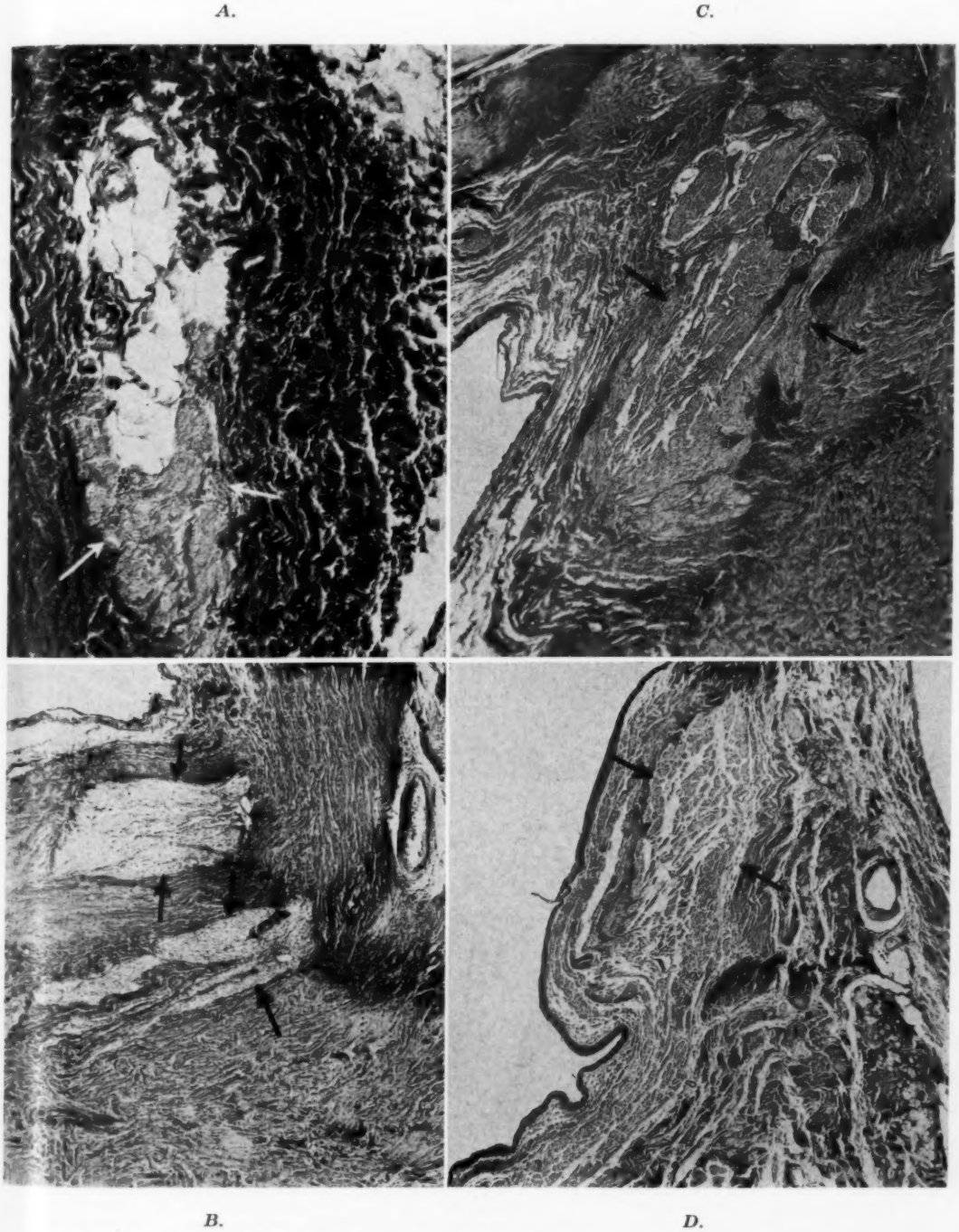


Fig. 9.—A-V bundle (Weigert-van Gieson stain). *A*, Beginning of penetrating portion (× 160). *B*, More distal part of penetrating portion (× 42). *C*, Most distal part of penetrating portion (× 48). *D*, Branching portion (× 45). Arrows point to the bundle. (Reduced by ¼.)

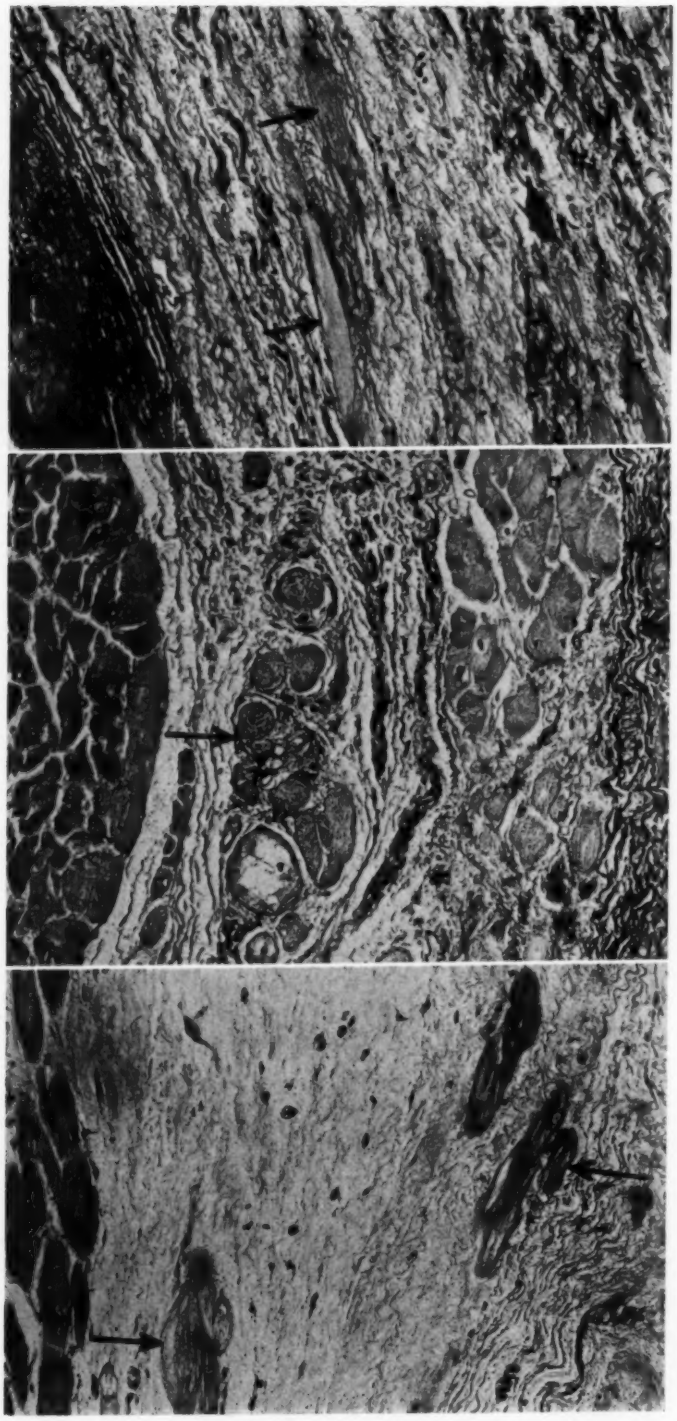


Fig. 10.—Left bundle branch. *A*, In proximal portion showing scattered fibers in a sea of elastic and collagenous fibers with scattered lymphoid cells (Weigert-van Gieson stain, × 160). *B*, More distal portion showing Purkinje fibers in various states of acute degeneration (Weigert-van Gieson stain. × 160). *C*, Peripheral Purkinje fibers with destruction of elastic and collagenous fibers and an infiltration of lymphoid cells (hematoxylin-eosin stain. × 140). Arrows point to left bundle branch. (Reduced ⅓.)

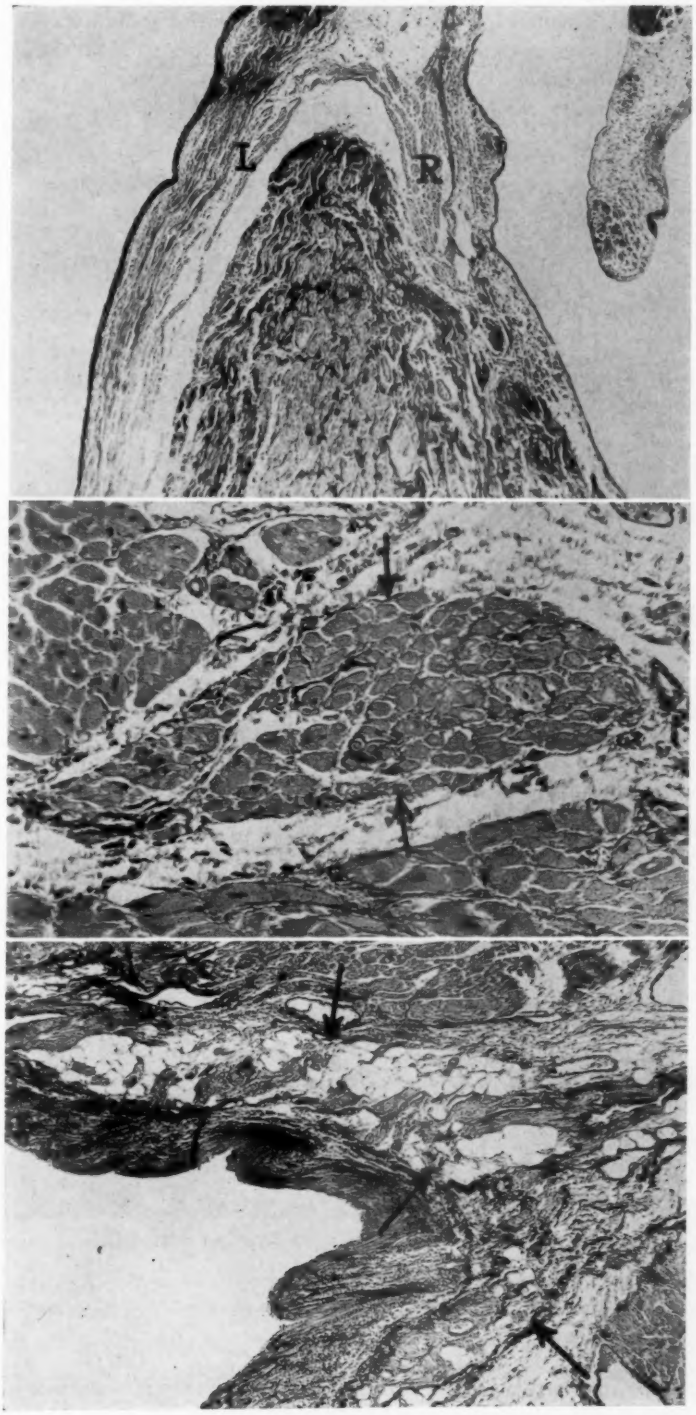
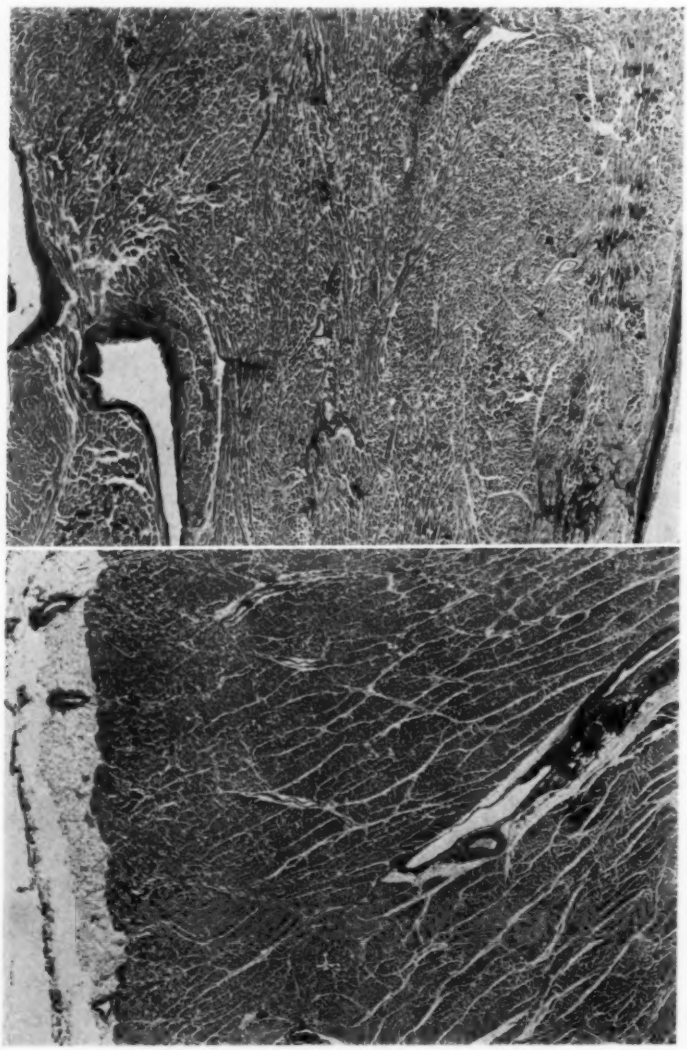


Fig. 11.—Right bundle branch (Weigert-van Gieson stain). *A*, At bifurcation (× 45). *B*, Intramyocardial portion (× 140). *C*, Distal portion (× 48). R = right bundle branch; L = left bundle branch. Arrows point to right bundle branch. (Reduced ¼.)

Atrial septum: The proximal part of the atrial septum presented striated muscle only in its upper part. This was reflected from the musculature of the markedly hypertrophied posterior crest. In the middle and lower aspects of the septum the wall consisted of fat tissue lined by markedly thickened endocardium presenting endocardial hypertrophy, especially of the smooth muscle type, and tremendous sclerotic changes, with large zones of calcification.

A.



B.

Fig. 12.—Left ventricular myocardium (Weigert-van Gieson stain). *A*, Subendocardial portion (× 16). *B*, Subepicardial portion (× 16). Fibrosis is present mostly in the subendocardial portion. (Reduced ¼.)

A-V node and its approaches, A-V bundle, bundle branches, and Purkinje network: As one approached the region of the insertion of the eustachian valve and the opening of the coronary sinus, one noted that the entire atrial septum was almost devoid of striated muscle (Fig. 7). It consisted of fat and fibrous tissue covered by markedly thickened endocardium. This endocardium showed a marked endocardial hypertrophy on both left and right sides with a marked smooth muscle hypertrophy. Likewise there was marked sclerosis with fibrosis and calcification. This

state continued into the actual regions where the A-V node should have been. Here a small rim of striated muscle hugged the base of the tricuspid valve. It was markedly fibrotic and distally became replaced completely by connective tissue.

The A-V node was found to be absent (Fig. 8). In its place there was scar tissue and fat tissue. The ramus septi fibrosi presented no change. The bundle of His began in the proximal right upper portion of the central fibrous body, without any antecedent node (Fig. 9, *A*). It thus had no connection with any atrial musculature. The cells of the beginning of the bundle were larger than normal, but distally the bundle took on its usual characteristics (Fig. 9, *B* and *C*). The branching portion of the bundle was normal (Fig. 9, *D*). The posterior radiation of the left bundle branch was embedded in an increased amount of elastic and collagenous tissue and there was focally considerable replacement of its substance with scar formation (Fig. 10). This was true both in its upper portion and in its distal Purkinje ramifications. Focally, the distal ramifications of the left bundle branch presented an infiltration of neutrophils and lymphoid cells (Fig. 10, *C*). The anterior radiation likewise was embedded in an increase in connective tissue. The right bundle branch and its ramifications presented no change (Fig. 11).

Free wall of left ventricle: The inner half of the wall presented irregular staining and smudging of many of the muscle fibers. In addition, there was an increase in connective tissue, with small scars and small organizing infarcts in this region, with an occasional scattering of plasma cells. The above changes were more marked in the anterior than in the posterior wall (Fig. 12). There were early necrotic changes in the arterioles, but there was no arteriolosclerosis.

Free wall of right ventricle: There was a slight increase in connective tissue throughout, with an occasional small organizing infarct. This was more marked in the inferior than in the anterior wall. In addition, there was a fine dispersion of lymphoid cells and an infiltration of an occasional neutrophil. There were early necrotic changes in the arterioles.

Ventricular septum: The ventricular septum presented a diffuse fibrosis with small scars and organizing infarcts, especially subendocardially on both sides.

Cardiac Pathologic Diagnoses.—(1) Congenitally malformed heart—abnormally formed atria and atrial septum; abnormally formed limbus and fossa ovalis; abnormally formed eustachian valve; abnormally formed conus. (2) Marked fibrosis, fatty infiltration, and calcification of the atria with absence or replacement of muscle. (3) Partial fibrosis of S-A node. (4) Absence or fibrosis of A-V node. (5) Absence of communication between atrial musculature and the bundle of His. (6) Focal fibrosis of the left bundle branch and Purkinje network. (7) Fibrosis with small scars of inner parts of walls of both ventricles and the ventricular septum. (8) Hypertrophy and dilatation of the heart—all chambers, especially right atrium and ventricle. (9) Marked endocardial sclerosis with calcification of both atria, and to a lesser extent of both ventricles. (10) Acute degeneration of the myocardium, left ventricle, inner wall. (11) Acute arteriolar degeneration.

DISCUSSION

It is clear that the atrioventricular block in this case is related to the absence of a muscular connection between the atrial musculature and the atrioventricular conduction system. The muscular approaches to the A-V node are absent and the A-V node itself is either congenitally absent or replaced by scar tissue. As such, this type of block represents a most unique circumstance. Most congenital or acquired atrioventricular blocks are related to pathologic change in the A-V node and/or bundle, or in both bundle branches. We have been able to find only one case of acquired heart disease (Oppenheimer and Oppenheimer[23]) in which the A-V node was separated from the auricular tissue by fibroadipose tissue, and one case (Wallgren and Winblad,[7] Case 2) of congenital heart disease in which the A-V node was apparently absent and the atria were separated from the remnant of the A-V bundle. Our case differs from the latter in that the latter was associated with a patent foramen primum.

As to the basic nature of the pathologic process leading to the block in our case, there is evidence that there was an abnormality in formation of the atria. This is seen in the absence of musculature in that part of the right atrium derived from the sinus venosus. It is therefore possible that there was an abnormality in the absorption of the sinus venosus. In favor of this hypothesis is the abnormal eustachian valve and the abnormal architecture of the limbus fossa ovalis, derived from the septum secundum, one component of which is derived from the sinus valves.

According to this viewpoint, we would be dealing with congenital atrioventricular block. It is possible that continuity between the S-A and A-V nodes was originally present, but, because of the abnormality in formation of the atria, fibrosis and destruction of muscle led to secondary destruction of the A-V node and its connections after birth. This would then represent acquired heart block in congenital heart disease. Or it is possible that the A-V node, originally well formed in the atrioventricular canal at 8 to 10 mm.,[24-28] was secondarily destroyed and its atrial attachments compromised as the contiguous sinus venosus (coronary sinus region) was aberrantly incorporated into the atrium at 10 to 12 mm. The importance of the approaches to the A-V node in the genesis of block has been theoretically postulated by Mahaim[10] in congenital block, and by Kung and Mobitz[29] in acquired block.

Congenital atrioventricular block is relatively uncommon. The literature on this subject has been repeatedly reviewed.[3-7,10-13,30] It has been described in patent foramen primum,[5,7] transposition of the atria and ventricles,[3,8,31] cor biatriatum triloculare,[2,32] large ventricular septal defect,[4,9,33-35] cor triloculare biventriculosum,[6] or in otherwise apparently normally formed hearts.[7] In these conditions the conduction system has been studied. Here disruptions in continuity, either congenital or fibrotic, have been described between the A-V node and bundle, or within the atrioventricular bundle, and in one case between the auricles and the bundle of His. In addition to these conditions, complete atrioventricular block has been described in the following conditions in which no conduction system studies have as yet been made: congenital aneurysm of the pars membranacea,[36] tricuspid atresia,[37-39] mitral atresia,[13] tetralogy of Fallot,[40] Eisenmenger complex,[12] bicuspid aortic valve with sclerosis and calcification,[41] fibroelastosis,[42,43] and fetal coarctation.[44,45] In addition to the case of Wallgren and Winblad, two other normally formed but enlarged hearts have been the seat of congenital heart block.[46,47]

It is possible, of course, that this heart falls into the category of acquired heart block in which some pathologic process has acted mostly on the atria rather than the ventricles. Acquired heart block has been described in rheumatic[10,16,48,49] and syphilitic heart disease,[10,16,50-52] hypertensive and coronary heart disease,[10,16] sclerosis of the mitral and aortic annulus,[20] tumors,[53,54] myocarditis of various etiology,[10,16,55-74] and in fatty infiltration.[10,15,16] Of all these, the closest to our case might be myocarditis or fatty infiltration. Myocarditis involving the S-A and A-V nodes predominantly has been described. However, in our present knowledge, replacement of myocardium by fat tissue does not fall into the realm of myocarditis. Fatty infiltration by itself usually involves the A-V node, bundle,

and the beginning bundle branches. It is usually, however, not associated with fibrosis and calcification of the atria. Hence, acquired heart block, not related to congenital heart disease, is unlikely in our case.

The considerable hypertrophy of the heart in this case, especially the right ventricle, is not clearly understood in the absence of primary pulmonary changes, valvular pathology, diastolic hypertension or coronary disease. It is possible that the high pulse pressure so characteristic of complete atrioventricular block, acting over a long period of time, may lead to marked hypertrophy. The elucidation of this problem requires the study of a large series of hearts of long-standing atrioventricular block.

SUMMARY

A case of complete heart block of 42 years' known duration is presented with a detailed histopathologic study of the conduction system, the atria and ventricles. This study revealed a complete lack of connection between markedly defective atrial musculature and the bundle of His, in the absence of the A-V node. This was associated with marked pathologic changes in the atria. It is suggested that these changes are due to a congenital malformation of the atria, and hence that we are dealing with either congenital heart block, or congenital heart disease with acquired heart block.

Acknowledgment is made to Mr. John T. Thomas, B.S., M.T., A.S.C.P., for his technical assistance.

REFERENCES

1. Benjamin, J. E., and White, P. D.: J.A.M.A. **149**:1549, 1952.
2. Wilson, J. G., and Grant, R. T.: Heart **12**:295, 1925.
3. Yater, W. M.: Am. J. Dis. Child. **38**:112, 1929.
4. Yater, W. M., Lyon, J. A., and McNabb, P. E.: J.A.M.A. **100**:1831, 1933.
5. Yater, W. M., Barrier, C. W., and McNabb, P. E.: Ann. Int. Med. **7**:1263, 1934.
6. Yater, W. M., Leaman, W. G., and Cornell, V. H.: J.A.M.A. **102**:1660, 1934.
7. Wallgren, A., and Winblad, S.: Acta paediat. **20**:175, 1937-38.
8. Uher, V.: Frankfurt. Ztschr. Path. **49**:349, 1936.
9. Turpin, R., Lenègre, J., and Chassagne, P.: Arch. franç. pédiat. **4**:617, 1947.
10. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, 1931, Masson et Cie.
11. Campbell, M., and Suzman, S. S.: Am. Heart J. **9**:304, 1934.
12. Campbell, M., and Thorne, M. G.: Brit. Heart J. **18**:90, 1956.
13. Donoso, E., Braunwald, E., Jick, S., and Grishman, A.: Am. J. Med. **20**:869, 1956.
14. Krumbhaar, E. B.: Univ. Pennsylvania M. Bull. **21**:278, 1908-09.
15. Nuzum, F.: Arch. Int. Med. **13**:640, 1914.
16. Mönckeberg, J. G.: Untersuchungen über das Atrioventrikularbündel im menschlichen Herzen, Jena, 1908, G. Fischer.
17. Mönckeberg, J. G.: Die Missbildungen des Herzens, In Handbuch der Speziellen Pathologischen Anatomie und Histologie **11**:1, Berlin, 1924, Springer & Co.
18. Cordero, A.: Ztschr. Kreislaufforsch. **26**:288, 1934.
19. Yater, W. M., Cornell, V. H., and Claytor, T.: Arch. Int. Med. **57**:132, 1936.
20. Yater, W. M., and Cornell, V. H.: Ann. Int. Med. **8**:777, 1935.
21. Fiorio, G.: Arch. "de Vecchi" anat. pat. e med. clin. **2**:441, 1940.
22. Rossi, L.: Sc. med. ital., 2nd series **3**:514, 1955.
23. Oppenheimer, A., and Oppenheimer, B. S.: Arch. Int. Med. **13**:957, 1914.
24. Walls, E. W.: J. Anat. **81**:93, 1947.
25. Mall, F. P.: Am. J. Anat. **13**:249, 1912.
26. Shaner, R. F.: Anat. Rec. **44**:85, 1929.
27. Sanabria, T.: Arch. de biol., Paris **47**:1, 1936.
28. Field, E. J.: Brit. Heart J. **13**:129, 1951.
29. Kung, S. K., and Mobitz, W.: Arch. exper. Path. u. Pharmakol. **155**:295, 1930.

30. Mathieu, L., Pierquin, L., and Botkovitz, F.: Rev. méd. de Nancy **65**:467 and 515, 1937.
31. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association, p. 58.
32. Abbott, M. E., and Moffatt, D.: Cited by Abbott, M. E.: In Nelson Loose Leaf Medicine, Section on Congenital Heart Disease, New York, 1932, Thomas Nelson & Sons, Vol. 4, p. 210.
33. Josué, O.: Bull. et mém. Soc. méd. hôp., Paris **43**:408, 1919.
34. Perotti, D.: Bol. Soc. med.-chir. di Pavia, **3**(N.S.):1, 1928.
35. Rogers, H. M., and Rudolph, C. C.: Am. Heart J. **41**:770, 1951.
36. Clark, R. J., and White, P. D.: Circulation **5**:725, 1952.
37. Dickson, R. W., and Jones, J. P.: Am. J. Dis. Child. **75**:81, 1948.
38. Aitchison, J. D., Duthie, R. J., and Young, J. S.: Brit. Heart J. **17**:63, 1955.
39. Hoekenga, M. T.: Am. J. Dis. Child. **69**:231, 1945.
40. Bernreiter, M., and O'Connell, F.: J.A.M.A. **150**:792, 1952.
41. Clark, R. J., and Firminger, H. I.: New England J. Med. **240**:710, 1949.
42. Rotem, J.: Ann. paediat. **175**:65, 1950.
43. Stadler, H. E., Reid, C. A., and Friedman, H. P.: J. Pediat. **36**:370, 1950.
44. Wendkos, M. H., and Study, R. S.: Am. Heart J. **34**:138, 1947.
45. Witt, D. B.: Am. J. Dis. Child. **47**:380, 1934.
46. Plant, R. K., and Stevens, R. A.: Am. Heart J. **30**:615, 1945.
47. Maclellan, E. K.: Brit. M. J. **1**:14, 1935.
48. Gross, L., and Fried, B. M.: Am. J. Path. **12**:31, 1936.
49. Crawford, J. H., and Di Gregorio, N. J.: Am. Heart J. **34**:540, 1947.
50. Rosenthal, S. R.: Arch. Int. Med. **50**:730, 1932.
51. Braunstein, A. L., Bass, J. B., and Thomas, S.: Am. Heart J. **19**:613, 1940.
52. Sohval, A. R.: Arch. Path. **20**:175, 1935.
53. Mahaim, I.: Les tumeurs et les polypes du coeur, Paris, 1945, Masson et Cie.
54. Leicher, F.: Ztschr. Kreislaufforsch. **37**:105, 1948.
55. Marvin, H. M.: Am. J. Dis. Child. **29**:433, 1925.
56. Hume, W. E.: Heart **5**:25, 1913-14.
57. Fleming, G. B., and Kennedy, A. M.: Heart **2**:77, 1910-11.
58. Stecher, R. M.: Am. Heart J. **4**:545, 1929.
59. Reid, W. D.: Am. Heart J. **5**:524, 1930.
60. Neubauer, C.: Brit. J. Child. Dis. **40**:93, 1943.
61. Massey, F. C., and Walker, W. J.: Arch. Int. Med. **81**:9, 1948.
62. Engle, M. A.: Pediatrics **3**:222, 1949.
63. Bernstein, M.: Am. Heart J. **16**:582, 1938.
64. Paul, W. D., Rhomberg, C., and Cole, J.: Am. Heart J. **31**:138, 1946.
65. Dassen, R.: Am. J. M. Sc. **186**:499, 1933.
66. Swift, E. V., and Smith, H. L.: J.A.M.A. **109**:2038, 1937.
67. Logue, R. B., and Hanson, J. F.: Am. Heart J. **30**:205, 1945.
68. Rantz, L. A., Spink, W. W., and Boisvert, P. J.: Arch. Int. Med. **77**:66, 1946.
69. Menon, T. B., and Rao, C. K. P.: Am. J. Path. **21**:1193, 1945.
70. Rosenberg, D. H.: Proc. Soc. Exper. Biol. & Med. **58**:9, 1945.
71. Clark, N. S.: Arch. Dis. Childhood **23**:156, 1948.
72. Kanatsoulis, A.: Arch. mal. coeur. **41**:250, 1948.
73. Rawkins, M. D., and Konstam, G. L. S.: Lancet **2**:152, 1949.
74. Cowan, J., Fleming, G. B., and Kennedy, A. M.: Nodal Rhythm and Heart Block in Acute Infection, 17th International Congress of Medicine, Section 6, Medicine, London, 1913.

The Significance of Atrioventricular Block Complicating Acute Myocardial Infarction

Donald B. Cohen, M.D., LeRoy Doctor, M.D., and Alfred Pick, M.D., Chicago, Ill.

The occurrence of second degree and complete atrioventricular (A-V) block in acute myocardial infarction has been considered generally a poor prognostic sign. The immediate mortality rates are reported to be considerably higher in cases with acute myocardial infarction complicated by A-V block than in those without block. Katz and Mintz[1] calculated mortality rates of 54.6 and 100 per cent in second degree and complete blocks, respectively. Master[2] noted 33 per cent mortality in partial block and 67 per cent mortality in complete heart block. However, the number of cases included in both of these series was small. Master also reported that first degree A-V block has little effect on the prognosis of acute myocardial infarction. He found the incidence of second and third degree A-V block occurring in the course of acute myocardial infarction to be 3 and 1.2 per cent, respectively.

The purpose of this study is to define the immediate and long-term prognosis of myocardial infarction with this complication in a series larger than previously reported, and to point out some related factors which may directly affect the mortality and survival.

MATERIAL AND METHODS

The present series comprises 68 cases in which a second degree A-V block or A-V dissociation due to A-V block were recorded in serial electrocardiograms in the course of acute myocardial infarction. The patients were selected from the files of the Heart Station of the Michael Reese Hospital, on the basis of the electrocardiographic evidence. The clinical and follow-up data were obtained from the Medical Records Room of the Michael Reese Hospital, from the attending staff of Michael Reese Hospital, and, in some cases, from information received directly from the patients or their families. The follow-up period after the acute infarction varied from 3 months to 11 years and 7 months. Information after the initial episode could not be obtained on 3 patients.

In our department, A-V block is classified as first degree, second degree, advanced second degree, and complete.[3] Cases exhibiting first degree A-V block were not included in this series. As opposed to second degree block with single dropped beats, the term "advanced second degree

---

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

Aided by the Michael Reese Research Foundation, and the National Heart Institute (H-2276).
Received for publication Aug. 14, 1957.

block" is applied to cases in which several successively dropped beats initiate A-V nodal escape and A-V dissociation with or without ventricular captures. The diagnosis of recent myocardial infarction was established in all patients on the basis of the correlation of electrocardiographic evidence with the clinical course. Seventeen patients were examined at autopsy, and the presence of recent infarction was demonstrated in each case.

RESULTS

The average age of the 68 patients in this series was 60.7 years, 43 being male and 25 female. The average age of the males was 58.4 years, and of the females, 65.0 years. On the basis of the electrocardiographic pattern, the posterior wall was shown to be the site of infarction in 51 (75 per cent), the anterior wall in 16 (24 per cent), and both anterior and posterior walls in 1 case.

Over-all mortality and survival rates of the patient material is shown in Table I. Thirty-two patients (47.1 per cent) died within 2 months of the acute attack. Of these, 12 had infarcts on the anterior wall, 19 on the posterior wall, and 1 on both anterior and posterior walls. Thus, of the 16 patients in the entire series who suffered anterior wall infarction with A-V block, 75 per cent died within a 2-month period; contrariwise, of the 57 with posterior wall infarction, only 37.3 per cent died within the same period.

TABLE I. MORTALITY AND SURVIVAL RATES IN ACUTE MYOCARDIAL INFARCTION COMPLICATED BY A-V BLOCK

PERIOD OF CLINICAL OBSERVATIONS	TOTAL CASES IN GROUP	MORTALITY		CASES UNABLE TO BE TRACED DURING PERIOD INDICATED	CASES FOLLOWED ONLY FOR PERIOD INDICATED, BUT KNOWN TO BE ALIVE	TOTAL CASES FOLLOWED WHOSE CONDITION WAS KNOWN	SURVIVAL	
		TOTAL CASES OF KNOWN DEATHS	DEATH RATE (%)				CASES KNOWN TO BE ALIVE AT END OF PERIOD	
							NUMBER	PER CENT
First 2 mo.	68	32	47.1	—	—	68	36	52.9
2 mo.-1 yr.	33	3	9.1	3	—	65	29	44.4
1-5 yr.	28	6	21.4	2	8	63	22	34.9
5-10 yr.	10	3	30.0	4	4	59	7	11.8
Over 10 yr.	2	1	50.0	1	1	58	1	1.7

As shown in Table II, the immediate mortality rate increases with increasing degrees of A-V block. Thus, the death rate for second degree block was 33 per cent, for advanced second degree, 50 per cent, and for complete block, 77 per cent.

TABLE II. MORTALITY RATES IN DIFFERENT DEGREES OF A-V BLOCK

DEGREE OF A-V BLOCK	TOTAL NUMBER CASES	IMMEDIATE (2 MONTHS) MORTALITY
Second	33	11 (33%)
Advanced Second	22	11 (50%)
Complete	13	10 (77%)

Nine cases showed evidence of recent bundle branch system block. In 4 the block was right-sided; in 1, left-sided; in 3 it was indeterminate; and in 1 it shifted between right and left. Of these 9, 7 (78 per cent) died within a 2-month period. In the cases with advanced or complete block, the ventricular pacemaker was above the bifurcation of the common A-V bundle in 25 cases, below in 5, alternately above and below in 3, and indeterminate in 2. Of the 25 in which the pacemaker was above the bifurcation, 12 (48 per cent) died within 2 months; of the 10 in which it was below the bifurcation, 8 (80 per cent) died within this period. Ventricular rate was noted in all cases of advanced second degree and complete A-V block. Sixteen patients had ventricular rates of less than 40 per minute; 9 (56.3 per cent) of these died. Nineteen patients had ventricular rates over 40; 12 (63.2 per cent) died.

Thirty-six patients survived 2 months or more following infarction complicated by A-V block. In 32 of these patients the block was transient, the majority lasting less than 2 weeks; in 31, the infarct was located in the posterior wall. Of the 32 patients who died within 2 months of their infarct, 28 had A-V blocks which persisted until death. The posterior wall was the site of infarction in the 4 patients who died after the A-V block disappeared. Two of these patients had severe diabetes, and 1 had previous evidence of coronary artery disease. Of the 13 deaths known to have occurred in the group surviving 2 months or longer, 8 were due to another infarct, 2 to congestive heart failure, 1 to carcinoma of the liver, and 1 to pneumonia. In 1, the cause was unknown.

Previous evidence of myocardial infarction or chronic coronary insufficiency was present in 17 of the total group. Eleven died within 2 months, an immediate mortality rate of 64.7 per cent. Diabetes was present in 9 patients, 7 of whom died within 2 months, giving an immediate mortality of 77.7 per cent. Nineteen patients had previous evidence of hypertension; 13 died within 2 months after their attack of acute myocardial infarction, a mortality rate of 68.4 per cent. Nine patients had been taking digitalis before their acute attack; all of these died during the acute phase of their illness.

Long-term survival rates are shown in Table I. Of those followed for a period of 2 months to 1 year after the onset of their acute infarction, 44.4 per cent survived; from 1 year to 5 years, 34.9 per cent survived; from 5 years to 10 years, 11.8 per cent survived; and 1 patient was known to be alive for over 10 years (1.7 per cent survival).

Seventeen autopsy reports were available on patients who died within 2 months of infarction complicated by block. In all of these the last electrocardiogram before death showed persistence of the A-V block. In 16 of these patients there was involvement of the interventricular septum by the acute infarct. One autopsy was available on a patient who died 4 years after a myocardial infarction with a transient block. In this case the septum was not involved by the infarct.

DISCUSSION

The age and sex distribution in this series is similar to that found in previous series of myocardial infarction of all types from this hospital.[1] However, infarctions which are complicated by A-V block occur much more frequently on the

posterior wall than do infarctions in general.[4] Accordingly, posterior wall infarction was represented in this series with much higher frequency (75 per cent) than found in other series (20 to 40 per cent) which included myocardial infarctions of all types.[1,4]

The immediate mortality of acute myocardial infarction complicated by second degree, advanced, and complete A-V block was found to be higher than figures reported by others[1,5] for acute myocardial infarction in general. In this group, 47.1 per cent died within the first 2 months, as compared with a 27.6 per cent mortality in a study of all types of infarcts.[5] Furthermore, the mortality rate seems to be greater if the infarct complicated by block is on the anterior wall than if it is on the posterior wall, the percentages being 75.0 and 37.3, respectively. However, the mortality for posterior wall infarct with block is also greater than for posterior wall infarction in general,[5] illustrating the significance of this complication.

The immediate mortality increases with increasing degrees of block. Second degree block had a 33 per cent mortality; advanced second degree, 50 per cent; and complete A-V block, 77 per cent. Acute onset of bundle branch system block, which like an A-V block implies involvement of the interventricular septum,[6] appears to be associated with a high mortality. If in cases of advanced or complete block the ventricular pacemaker originates below the bifurcation of the common A-V bundle, the immediate mortality rate is increased. However, contrary to previous findings,[2] our data indicate that the ventricular rate per se has no significant effect on immediate or long-term prognosis of infarcts with A-V block.

Differences in the effect of transient and permanent block on the mortality rate of infarcts are difficult to assess, as the duration of the conduction disorder cannot be ascertained in individuals dying in the acute stage. However, if it is assumed that permanent A-V block is the result of actual destruction of the conduction fibers, and that transient block is a result of the conduction fibers being in the area of ischemia or edema surrounding the actual infarction, our post-mortem findings would suggest that 16 of 17 patients would have developed permanent A-V block, if all had survived. In keeping with such an assumption would be the fact that, of the 36 patients who survived the initial 2-month period following infarction, the block was transient in 32. Furthermore, in the single patient in this group who was autopsied, no involvement of the septum was found. It appears then that the over-all poor prognosis in infarction with A-V block may be caused by those cases in which the A-V conducting system is actually involved in the necrotic area, manifested in the electrocardiogram as a persistent A-V block.

Analysis of clinical data revealed that, as with myocardial infarction in general, other factors affected the prognosis of myocardial infarction complicated by A-V block. As previously shown,[1,4,5] diabetes, hypertension, previous infarcts, and the use of digitalis (as indication of heart disease preceding the infarction) were aggravating factors with regard to the immediate prognosis. However, the surviving groups in these categories were too small to permit an evaluation of their long-term prognosis.

A transient A-V block seems to have little effect on the long-term survival rate of patients with acute infarctions. In our series there is a survival rate of 44.4 per cent at the end of 1 year, and 34.9 per cent at the end of 5 years, as compared to Katz[5] and co-workers' figures of 55.0 and 16.2 per cent, respectively, for an unselected series of myocardial infarctions previously studied at Michael Reese Hospital.

SUMMARY AND CONCLUSIONS

1. Sixty-eight cases of acute myocardial infarction complicated by high degrees of A-V block have been analyzed. This complication is found more frequently with posterior than with anterior wall infarction.

2. The immediate mortality rate of infarction with second degree, advanced second degree, and complete A-V block exceeds that of myocardial infarction in general, especially if the infarct is located in the anterior wall and the block is due to necrosis of the ventricular septum. The mortality rate increases with the severity of the block.

3. The prognosis of myocardial infarction complicated by A-V block is further aggravated by factors known to be of importance in determining the immediate mortality rate of infarction in general.

4. In patients surviving the initial episode the long-term prognosis is not affected by persistence of an A-V block.

We are indebted to the physicians who permitted us to study the records of their cases, and to Dr. O. Saphir for use of the autopsy reports.

REFERENCES

1. Mintz, S. S., and Katz, L. N.: Arch. Int. Med. **80**:205, 1947.
2. Master, A. M., Dack, S., and Jaffe, H. L.: Am. J. M. Sc. **196**:513, 1938.
3. Katz, L. N., and Pick, A.: Clinical Electrocardiography, Part I, The Arrhythmias, Philadelphia, 1956, Lea & Febiger.
4. Cole, D. R., Singian, E. B., and Katz, L. N.: Circulation **9**:321, 1954.
5. Katz, L. N., Mills, G. Y., and Cisneros, F.: Arch. Int. Med. **84**:305, 1949.
6. Osher, H. L., and Wolff, L.: Am. Heart J. **45**:429, 1953.

The Spatial Vectorcardiogram in Complete Left Bundle Branch Block With Special Reference to the Initial Component

George W. Frimpter, M.D., Lawrence Scherr, M.D.,** and David Ogden, M.D.****
New York, N.Y.

The mechanism of production and clinical significance of bundle branch block has provoked considerable interest among clinicians and investigators during the last 2 decades. It is the primary purpose of this paper to call attention to the initial component in complete left bundle branch block (LBBB) and its probable significance.

The QRS configuration of LBBB was first defined by Wilson.[1] That is, a QRS duration of at least 0.12 second, delayed activation of the epicardial surface of the left ventricle, and initial positivity in the left ventricular cavity. Wenner and associates,[2] studying the esophageal lead in LBBB, noted that in 9 of 15 cases a minute Q wave preceded the positive deflection. The esophageal lead at the atrial level was considered by these investigators to be, in effect, a left ventricular cavity lead. Sodi-Pallares and co-workers,[3] using left and right intraventricular cavity leads by catheter (in complete LBBB in human beings), demonstrated that the main component of septal depolarization takes place in a right-to-left direction, resulting in an initial R wave in the left ventricular cavity lead, or an R wave preceded by a slight initial negative deflection, depending on the position of the electrode. Similar results were obtained by those investigators[4] in experimental LBBB in animals. It was further noted that in incomplete LBBB, septal depolarization may proceed in both right-to-left and left-to-right directions.

In the scalar electrocardiograms (ECG) of LBBB there are usually small initial R waves in the early precordial leads, indicating an initial anterior vector. The study of Pantridge and associates[5] of the vectorcardiograms (VCG) in 28 patients with LBBB did not elaborate upon this earliest vector. Scherlis and Grishman[6,7] reported on the VCG in 14 patients with LBBB, but did not comment on the initial anterior vector other than to note its occasional absence. However,

---

From the Cardiovascular-Electrolyte Laboratory, Second (Cornell) Medical Division, Bellevue Hospital, New York City, and the Department of Medicine, Cornell University Medical College.
Received for publication July 16, 1957.

*This investigation was completed during author's tenure as Research Fellow, New York Heart Association. Present address: Veterans Administration Hospital, Portland 7, Oregon.
**Intern, Second (Cornell) Medical Division, Bellevue Hospital, New York City.
***Intern, Strong Memorial Hospital, Rochester, N.Y.

with esophageal leads at the atrial level, they noted that the initial deflection was positive, " . . . except for a few records in which a minute Q wave preceded the RS pattern."[6] It was felt that further elaboration of the initial deflection in LBBB with the aid of vectorcardiography might provide additional information relative to the mechanism of LBBB and the variation of electrocardiographic patterns seen therein.

Other authors have either denied or ignored the presence of an initial R over the right chest. Previous studies have indicated that such may be present or absent,[6,7] and no explanation as to the meaning of this wave has been offered. However, previous work has been limited by the use of bipolar or unipolar leads,[6] or primitive vector systems utilizing a "cube"[6] or "tetrahedron."[5]

The advent of a corrected lead system has now made it possible to obtain a picture of the orientation of the electrical forces in LBBB. We have used the system of Frank[8] to obtain an accurate representation of the vector forces. From such a study we believe we have obtained a better understanding of the ECG and some details of the underlying physiology in LBBB.

TABLE I. ANALYSIS OF MEAN SPATIAL VECTOR IN LEFT BUNDLE BRANCH BLOCK

PATIENT	AGE (YR.)	QRS DURATION (SEC.)	MEAN SPATIAL VECTOR					
			HORIZONTAL		FRONTAL		SAGITTAL	
			ANGLE (DEG.)	MAG. (MV.)	ANGLE (DEG.)	MAG. (MV.)	ANGLE (DEG.)	MAG. (MV.)
1.*	63	.16	290	2.7	0	0.9	180	2.3
2.*	65	.12	292	1.1	10	1.0	170	0.5
3.*	54	.13	284	1.3	23	0.5	175	1.5
4.*	63	.14	322	1.8	0	1.2	177	1.5
5.*	63	.16	280	1.8	325	0.4	175	1.9
6.	55	.12	278	1.8	40	0.3	175	1.5
7.	65	.14	300	1.3	35	0.8	160	1.1
8.	66	.17	315	1.4	40	1.1	145	1.1
9.	86	.14	300	1.2	340	0.9	185	1.0
10.	75	.13	282	1.7	347	0.7	176	1.5
11.	78	.13	305	1.4	10	1.1	166	1.1
12.	69	.13	290	1.2	295	0.8	215	1.5
13.	93	.13	310	1.6	3	1.2	177	1.3
14.	68	.15	300	1.5	40	0.8	165	1.4
15.	80	.14	285	2.0	80	1.3	140	2.2
16.	55	.14	285	2.1	330	0.8	180	2.0
17.	63	.15	300	2.3	0	1.2	180	2.0
18.	58	.12	295	1.1	345	0.7	175	0.9
19.	78	.13	290	1.4	55	1.1	150	1.6
20.	74	.13	300	1.2	345	0.7	188	1.0
21.	75	.14	300	1.5	320	0.8	190	1.1
22.	53	.16	275	0.6	285	0.7	230	0.9
23.	56	.17	310	1.9	5	1.3	175	1.5
24.	76	.13	331	1.3	27	1.3	136	0.8
25.	77	.12	333	1.9	253	0.9	180	1.2

*History compatible with myocardial infarction in past.

MATERIAL

Twenty-five patients with complete LBBB were studied (Table I). Electrocardiographic criteria for the diagnosis of complete LBBB were generally those of Wilson.[9] All cases had a QRS duration of at least 0.12 second and predominant positivity over the left ventricle. Records displaying initial negativity in Leads I, aV_L, V_5 or V_6 were not excluded if they had the general features of LBBB. A detailed clinical history was available in all cases. Patients 1 through 5 presented a history compatible with myocardial infarction in the past.

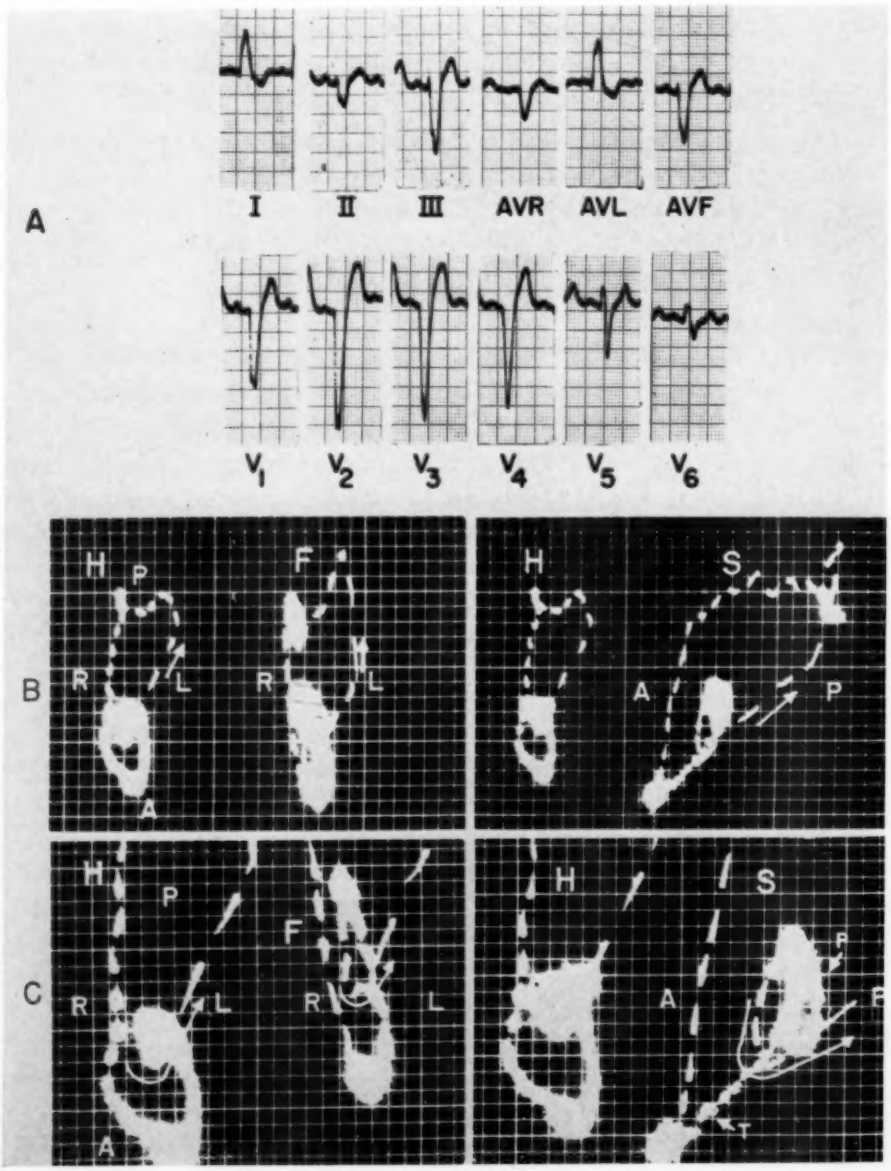


Fig. 1.—Case 22. *A*, ECG shows LBBB with Q in Leads I and aV_L. *B*, General configuration of planar projections of spatial VCG loops (*H*—horizontal; *F*—frontal; *S*—sagittal; *A*—anterior; *P*—posterior; *R*—right; *L*—left). *C*, Enlarged areas of activity about the isoelectric spot. Arrows indicate the initial anteroinferior vector which goes slightly to the right, giving rise to the Q in Leads I and aV_L.

METHODS

Electrocardiograms were recorded on a Sanborn Cardiette (photographic) or a Viso-Cardiette (direct writing), both utilizing a paper speed of 25 mm. per second and standardization of 1.0 mv. per cm., or 2.0 mv. per cm. where necessary.

Vectorcardiograms were recorded by the system of Frank[8] with the recommended method of placement of thoracic electrodes.

Pre-amplification was provided by Tektronix type 122 low-level amplifiers with frequency response set at 0.2 to 250 cycles per second. A DuMont type 322 oscilloscope utilizing a dual-beam cathode-ray tube allowed simultaneous recording of two planar projections on the spatial VCG. A selector switch allowed various combinations of horizontal, frontal, and sagittal projections. A Thyratron condenser circuit provided time markings of 0.004 second each, from the beginning of one to the beginning of the next, with the tear drop in the direction of travel. Standardization was then increased to provide amplification and permit study of the detail about the isoelectric spot. Occasionally, the upper limit of frequency response had to be lowered to 50 cycles per second to obtain good oscilloscopic tracings when electronic magnification was great. Multiple oscilloscopic tracings were photographed on 35 mm. Tri-X film, and were then enlarged with a table viewer for measurement of detail. Helm's modified triaxial reference system "A" was employed for spatial orientation and quantitative measurement of the vector angles.[10] The simultaneous recording of two planar projections was found to be a definite aid in analysis of the VCG.

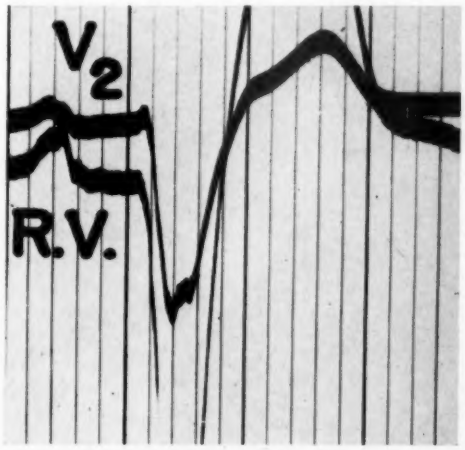


Fig. 2.—Case 22. **Negative right ventricular cavity lead is compatible with right-to-left depolarization of the intraventricular septum, and LBBB.**

RESULTS

The scalar ECG in 25 cases of LBBB studied revealed prolonged QRS complexes ranging from 0.12 to 0.17 second with a mean of 0.14 second. Electrocardiograms were evaluated chiefly for the presence of a Q wave in Leads I, aV_L, V_5, and V_6, and the presence of an R wave in Leads V_1 and V_2. In 6 of 25 cases, a Q wave was found in one or more of Leads I, aV_L, V_5 and V_6 (Figs. 1 and 2). In only 2 of these cases was there a clinical history of previous myocardial infarction.

Nineteen cases demonstrated an R wave in V_1 and/or V_2 (Fig. 3). In 2 additional cases, an R wave was preceded by a small Q wave in V_1 and/or V_2 (Fig. 4). The remaining 4 cases did not show an R wave in V_1 or V_2 (Fig. 5).

The VCG in LBBB can be best described by construction of the spatial QRS-T loop from the planar projections. The initial vector activity is usually anterior and somewhat to the left and downward. At times it may be slightly to the right and at times slightly upward. This anterior vector may not be present, as will be discussed later. Following the initial vector which is completed within 0.024 second, the spatial QRS loop moves rapidly posteriorly and to the

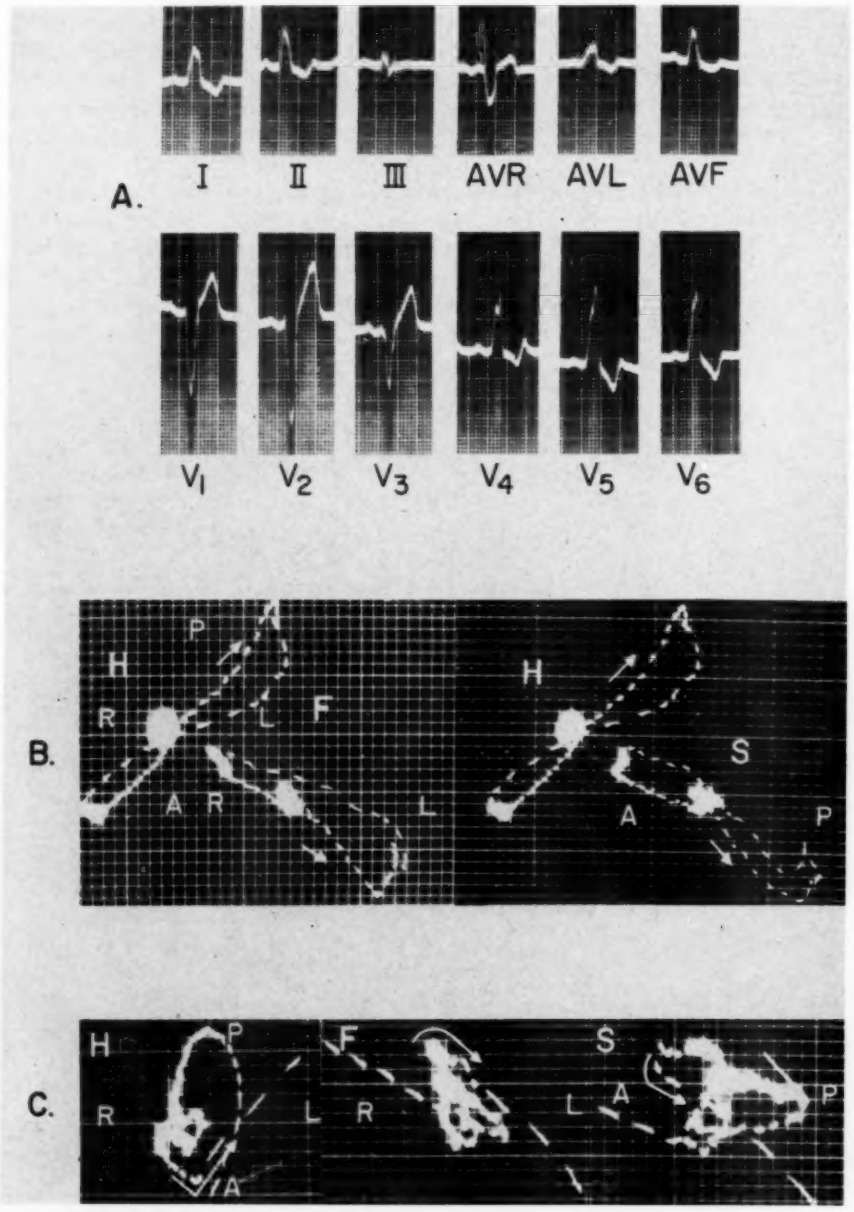


Fig. 3.—Case 8. *A*, ECG shows LBBB with small R waves in V_1 and V_2. *B*, Planar projections of spatial vector loops. *C*, Enlarged views show an initial vector anteriorly and to the left.

left, and usually inferiorly, then constantly arches superiorly and to the right and anteriorly. The spatial QRS loop is always incomplete; the T wave returns the composite QRS-T loop to the isoelectric spot.

Analysis of Initial Vector.—In 21 of 25 cases the QRS loop showed an initial anterior vector usually occurring within the first 0.024 second of ventricular depolarization. This initial vector was described in each plane by measuring the

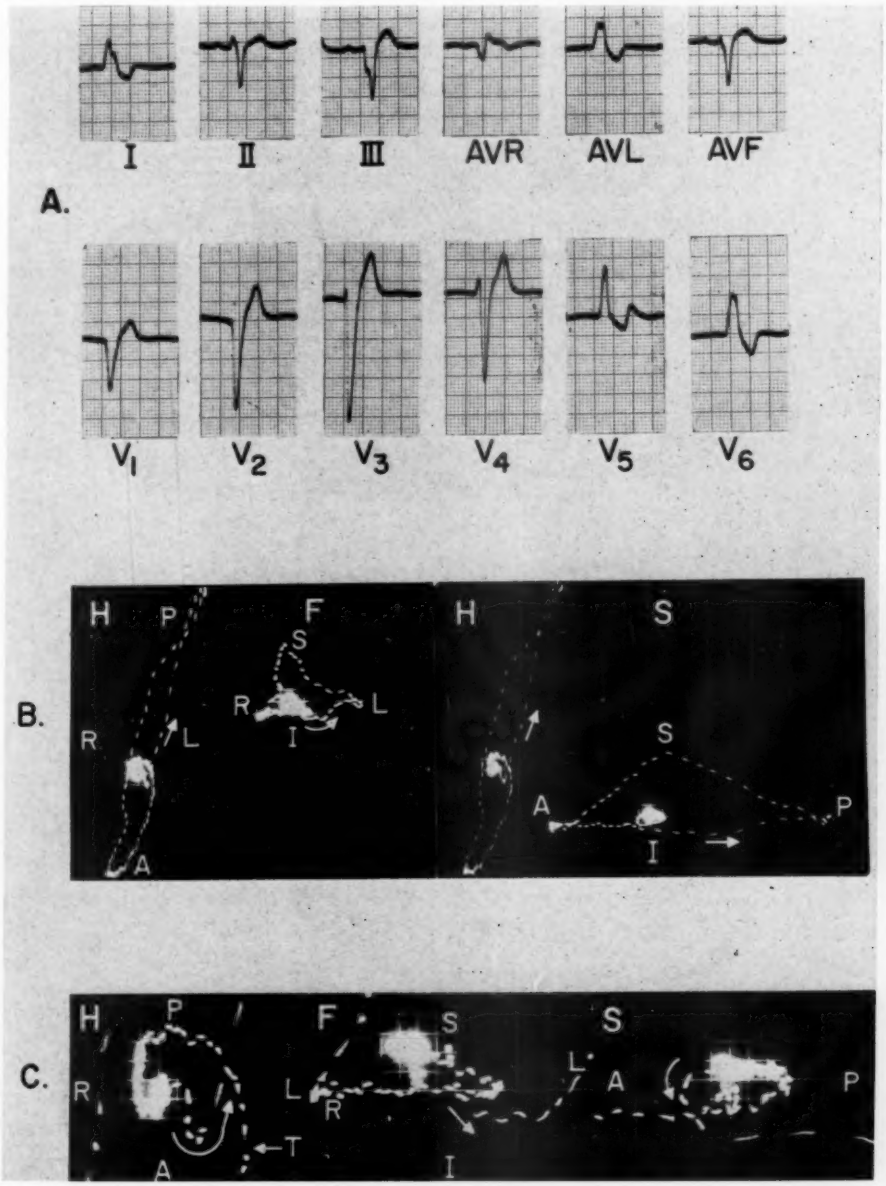


Fig. 4.—Case 1. *A*, ECG shows LBBB with a QRS pattern in V_1 and V_2. Precordial leads are ½ standardized. *B*, Planar projections of spatial vector loops. *C*, Enlarged views show how ECG pattern comes about. It is postulated that this may result from septal depolarization from right to left, followed by right ventricular activity and, finally, the depolarization of the left ventricular mass.

angle of the loop from the isoelectric point, at 0.004 second intervals. The angle and magnitude of the maximum initial deflection were also measured in three planar projections whenever feasible. Because of superimposition of oscilloscopic time markings, it was not always possible to analyze these initial vectors in every plane (Table II). In 4 of the 25 cases, no such initial anterior vector was visualized on the oscilloscope.

TABLE II. ANALYSIS OF INITIAL DEFLECTION OF VECTORCARDIOGRAM IN LEFT BUNDLE BRANCH BLOCK

PATIENT	MAXIMUM INITIAL DEFLECTION					
	HORIZONTAL		FRONTAL		SAGITTAL	
	ANGLE (DEG.)	MAG. (MV.)	ANGLE (DEG.)	MAG. (MV.)	ANGLE (DEG.)	MAG. (MV.)
1.	40	0.20	41	0.18	40	0.21
2.	Absent					
3.	90	0.11	*	*	10	0.09
4.	86	0.20	52	0.16	58	0.24
5.	55	0.17	*	*	7	0.15
6.	100	0.09	*	*	0	0.06
7.	Absent					
8.	90	0.09	330	0.04	0	0.10
9.	77	0.11	30	0.12	10	0.12
10.	75	0.16	*	*	345	0.15
11.	55	0.11	*	*	60	0.13
12.	123	0.10	*	*	40	0.10
13.	90	**	*	*	10	**
14.	25	0.26	*	*	70	0.28
15.	78	0.28	*	*	0	0.30
16.	Absent					
17.	90	0.10	*	*	0	0.17
18.	50	0.06	*	*	315	0.07
19.	55	0.23	*	*	57	0.23
20.	73	0.10	81	0.16	63	0.20
21.	**	**	60	0.07	95	0.11
22.	85	0.10	75	0.30	65	0.33
23.	75	0.19	*	*	30	0.19
24.	Absent					
25.	25	0.15	40	0.27	0	0.12

*Obscured.
**Very small, could not be measured.

The initial portion of the VCG can best be described by considering its projection in three planes as follows:

Horizontal: The initial vector in 14 cases which showed an anterior component was oriented chiefly to the left and anteriorly. The maximum angle of the initial vector from the isoelectric point varied from 25 to 123 degrees. The range of magnitude in this plane was 0.06 to 0.28 mv.

Frontal: Because the initial vector was directed anteriorly in many of the cases, much of the oscilloscopic tracing was superimposed on the isoelectric point, obscuring visualization in the frontal plane. Thirteen of 21 cases that showed an

initial anterior component in other views could not be quantitated in the frontal view because of this problem. The maximum angle of this initial vector in the remainder of the cases varied between 330 and 81 degrees. The magnitude of these vectors in this plane ranged from 0.04 to 0.30 mv.

Sagittal: The initial vector was best visualized in this plane and could be easily quantitated in each case. In 12 instances the initial component was directed anteriorly and inferiorly, anteriorly in 3 instances, anteriorly and superiorly in 2 cases, and in 1 case inferiorly and slightly posteriorly. The angles of the maximum initial vector ranged from 315 to 95 degrees. A magnitude varying from 0.06 to 0.33 mv. was recorded.

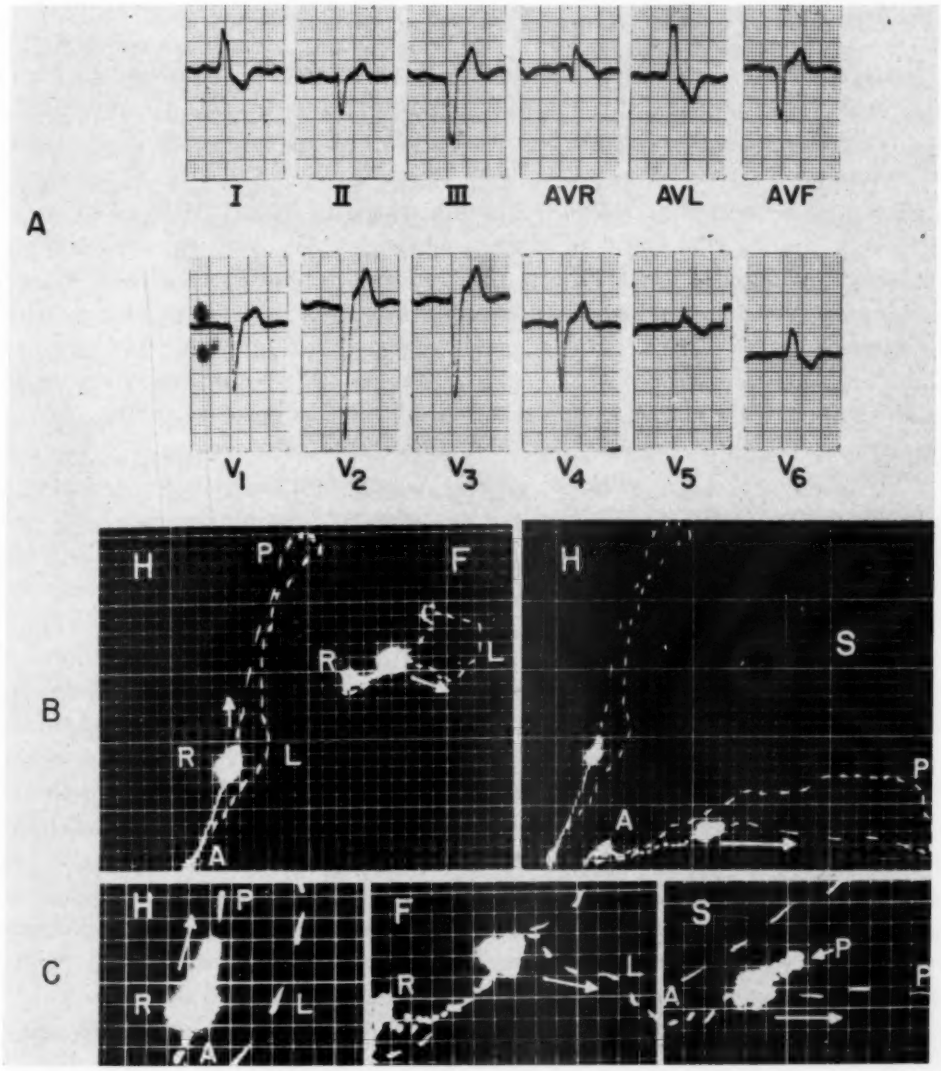


Fig. 5.—Case 16. *A*, ECG shows a Q in V_1 and V_2. Precordial leads are ½ standardized. *B*, General configuration of vector loops is similar to other cases. *C*, Enlarged views demonstrate the absence of an initial anterior vector. This is felt to be consequent to LBBB and a right ventricular conduction disturbance.

Correlation Between ECG and VCG.—In all of the 6 cases that illustrated a Q wave in one or more of the left ventricular leads, an initial anterior vector was present on oscilloscopic tracings (Fig. 1). There was no constant relationship between magnitude and angle other than anterior direction, in this particular group.

In all cases with an R wave in V_1 and/or V_2, the VCG revealed an initial anterior vector (Fig. 3). In 4 remaining cases where the ECG showed no R wave in V_1 and V_2, no initial anterior vector was seen on the VCG (Fig. 5).

No relationship was noted between the duration of the QRS complex and the presence or absence of an initial anterior component on the VCG.

DISCUSSION

Detailed analysis and quantitation of the vectorcardiograms of 25 patients with complete LBBB, including special attention to the initial component, have been presented. The results of this study differ in some aspects from those of other investigators.

First, the general spatial QRS-T loop configuration in LBBB was most constantly reflected by the sagittal projection (Figs. 1-5). Other workers[6,7] have emphasized the characteristics of the horizontal projections. However, in the present study the spatial loop was oriented in a nearly sagittal plane. Hence, little importance could be attributed to crossing, direction of rotation, or "figure-of-eight" appearance of the horizontal projection. The frontal loop was of value only in those instances in which the long axis of the spatial loop was oriented sufficiently to the left so that it was not superimposed upon itself.

Also, use of the VCG allowed analysis of the first 0.024 second of electrical activity at 0.004 second intervals; this detail was not possible by use of the routine ECG alone. An initial anterior vector was recorded in 84 per cent, or 21 cases, of this series. A vector oriented anteriorly during this early phase of ventricular depolarization would be expected to result in the initial positivity in V_1 and V_2. In normal ventricular conduction the septum depolarizing from left to right usually accounts for the aforementioned R wave. However, in LBBB septal depolarization is altered, and other explanations for this initial positivity can be postulated.

Sodeman and associates[11] attributed small R waves in leads from the right side of the precordium in LBBB to an initial positivity of the surface of the right ventricle. Myers[12] stated that right ventricular activation in LBBB is completed within 0.020 second, resulting in an R wave in the right precordial leads. Studies on experimental bundle branch block in dogs by Sodi-Pallares[3] indicated that unipolar leads from the left side of the septum in LBBB may be of the RS type, or they may show a small or even large initial negative deflection; however, the net effect is an RS intracavitary complex. Therefore, some of the septum may contribute to an initial anterior vector. It is thought, however, that this initial anterior vector is due primarily to the activity of the right ventricle.

In the 4 remaining cases of this series, no initial anterior vector was visualized (Fig. 5). These instances require further explanation. In LBBB the initial

component of the spatial VCG represents the vector sum of activity of the interventricular septum, depolarizing from right to left, plus the right ventricular mass with vector anteriorly.

In 84 per cent of cases this resulted in an anterior vector. However, the remaining cases are quite different in lacking this initial vector. It is unlikely that the septal activity would so completely dominate over the right ventricle, unless there was a delay in right ventricular activity. Therefore, it is postulated that in these cases lacking an initial anterior vector an associated right ventricular conduction defect co-exists with LBBB. If this be right bundle branch block, it must be incomplete, as human right bundle branch block may frequently be, or the impulse of supraventricular origin would not reach the ventricle and/or the QRS complex would simulate the atypical "intraventricular heart block." In LBBB the activity of the left ventricular mass would mask a delayed right ventricular activity. The net result would be an absence of the R wave in V_1 and V_2, and of the initial anterior vector in the VCG. Bilateral conduction defects may be more common than is generally appreciated, since left ventricular conduction defects can mask those of the right ventricle on ECG.

Cases 1 and 19 exhibited a unique QRS complex in the right precordial leads, consisting of a small Q wave, a small R wave, and a deep S wave (Fig. 4). The pattern of the vector in the first 0.024 second in both cases is consistent with this electrocardiographic finding, as illustrated in the transverse plane by a deflection first to the left and slightly posteriorly, then sharply anteriorly, and finally posteriorly. This phenomenon may represent the septum depolarizing from right to left prior to depolarization of the right ventricle. This is compatible with the observations of Sodi-Pallares[3,4] in which intraventricular leads were used.

In 6 cases demonstrating a Q wave in one or more of Leads I, aV_L, V_5 or V_6 (Fig. 1), no definite correlation with a history of a previous myocardial infaretion could be made. It is stated that a Q wave in left-sided precordial leads in LBBB is usually indicative of myocardial infarction.[1,4,7,13] Sodeman and associates[11] feel that the initial positivity of the surface of the right ventricle may under certain circumstances give rise to a Q wave in Lead I. However, Sodi-Pallares and colleagues[14] state that the exploring electrode, especially aV_L, may be oriented toward the left atrium, in which a complex of the QR type is seen in LBBB; this may result in a Q wave in this lead, even in the absence of a myocardial infarction. The orientation of the dipolar lead or exploring electrode in relation to the long axis of the initial anterior vector will determine the presence or absence of a Q wave, and will not necessarily be dependent upon the co-existence of myocardial infarction. Because pathologic examination was not obtained in this series, it cannot be guaranteed that these patients did not have myocardial infarction. However, on the basis of detailed clinical examination, only 2 of these 6 cases had a history compatible with myocardial infarction.

SUMMARY AND CONCLUSIONS

1. A detailed quantitative analysis of the VCG in 25 cases of LBBB was presented. For the first time, special attention was focused on the initial component of the VCG. The Frank system of electrode placement and the Helm

method of angular measurement permitted an accurate and consistent quantitation of the VCG.

2. Typically, the long axis of the vector was oriented posteriorly and to the left. The configuration in the horizontal plane was found to be variable. The sagittal projection was most consistent with respect to shape and direction of inscription.

3. The presence of an initial anterior component was in each case associated with an R wave in the right precordial leads. This was felt to be due primarily to right ventricular activity.

4. The occurrence of a Q wave in one or more of Leads I, aV_L, V_5 or V_6 in LBBB did not correlate with a history of previous myocardial infarction. The characteristics of the initial anterior vector may well explain the presence of this Q wave in the absence of myocardial infarction.

5. An explanation was offered for the occasional absence of the initial anterior vector. It was postulated that an associated right ventricular conduction defect may co-exist with LBBB in these cases.

We are indebted to the Allen B. DuMont Foundation for furnishing the oscilloscope used, and to Doctors Jerrold S. Lieberman and Albert L. Rubin for their assistance and encouragement. Cardiac catheterization was performed in Case 22 by Doctor J. Marion Bryant, Director of the Heart Station, Fourth (New York University) Medical Division, Bellevue Hospital, who kindly supplied the intraventricular ECG shown in Fig. 2.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliveira, R. M., Scarsi, R., and Barker, P. S.: Am. Heart J. **27**:19, 1944.
2. Wenner, J., Scherlis, L., and Sandberg, A. A.: Am. Heart J. **41**:864, 1951.
3. Sodi-Pallares, D., and Rodriguez, M. I.: Am. Heart J. **43**:27, 1952.
4. Rodríguez, M. I., and Sodi-Pallares, D.: Am. Heart J. **44**:715, 1952.
5. Pantridge, J. F., Abildskov, J. A., Burch, G. E., and Cronvich, J. A.: Circulation **1**:893, 1950.
6. Scherlis, L., and Grishman, A.: Am. Heart J. **41**:494, 1951.
7. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
8. Frank, E.: Circulation **13**:737, 1956.
9. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: Advances Int. Med. **2**:1, 1947.
10. Helm, R. A.: Circulation **13**:581, 1956.
11. Sodeman, W. A., Johnston, F. D., and Wilson, F. N.: Am. Heart J. **28**:271, 1944.
12. Myers, G. B.: Am. Heart J. **39**:817, 1950.
13. Rosenman, R. H., Pick, A., and Katz, L. N.: Am. Heart J. **40**:845, 1950.
14. Sodi-Pallares, D., Estandia, A., Soberón, J., and Rodriguez, M. I.: Am. Heart J. **40**:655, 1950.

Electrocardiographic Changes in Hypopituitarism of Pregnancy

W. F. Bernart, M.D., and A. M. de Andino, Jr., M.D., San Juan, Puerto Rico*

Post-partum pituitary insufficiency was introduced as a clinical entity by Sheehan,[1] in 1939. Numerous reports have appeared which adequately describe the clinical and pathologic findings[2-5] as well as the therapeutic approaches[6,7] to this form of anterior lobe hypopituitarism, but the electrocardiographic changes associated with this condition have been reported only infrequently.

Hypopituitarism secondary to post-partum necrosis is not uncommon in Puerto Rico.[8] Because of malnutrition and parasitic infestations in a large segment of the indigent population, moderate to severe anemia is a frequent finding. Post-partum hemorrhage—usually due to hemorrhage from retained placental parts, intrapregnancy hemorrhage, or in ruptured ectopic pregnancies—in an anemic patient would predispose her to severe shock with subsequent reduction of the blood supply to the pituitary. This may be followed by atrophy or necrosis of the adenohypophysis,[1] which results in anterior pituitary insufficiency.

A study of the electrocardiograms of a series of patients with well-documented hypopituitarism of pregnancy was undertaken. The clinical and pathologic findings will be the subject of another communication.[8]

MATERIAL AND METHODS

The clinical records of 34 cases of hypopituitarism of pregnancy have been carefully studied. Suitable electrocardiograms were obtained in 22 cases. The electrocardiographic tracings were read according to the generally accepted criteria.[9,10] Low voltage was present when the QRS deflections in each of the 3 standard limb leads was 5 mm. (0.5 mv.) or less. Because low voltage, on occasions, may result from an unusually placed mean electrical axis, an analysis of the precordial lead QRS deflections has been included, utilizing Lapin's criteria.[11] Significantly low voltage was considered present when the deflections of the QRS complexes in V_2, V_3, V_4, and V_5 were 9 mm. (0.9 mv.) or less, and when in V_6 they were 7 mm. (0.7 mv.) or less.

From the Departments of Medicine of the University of Puerto Rico School of Medicine and the San Juan City Hospital, San Juan, Puerto Rico.

Received for publication Aug. 2, 1957.

*Trainee, National Heart Institute, United States Public Health Service. Present address: University of Virginia Hospital, Charlottesville, Va.

Significantly low voltage of the P and T waves was considered present if the amplitude was 1 mm. (0.1 mv.) or less in each of the 3 standard limb leads. The criteria for abnormalities of the P-R and Q-T intervals were based on Ashman and Hull's table.[12] The electrical axis of the heart was determined from the unipolar extremity leads.[13]

TABLE I. AGE GROUPS AT TIME OF HEMORRHAGE AND ELECTROCARDIOGRAM

AGE GROUP (YEARS)	AT TIME OF HEMORRHAGE	AT TIME OF ECG
15–20	1	0
21–30	14	6
31–40	5	9
41–50	2	4
51–60	0	3
Total	22	22

TABLE II. THE INCIDENCE OF LOW VOLTAGE

	NUMBER OF CASES	PER CENT
QRS complexes		
Limb leads	3	13
Precordial leads*		
V_2	2	11
V_3	5	28
V_4	6	33
V_5	8	44
V_6	8	44
"Tendency to low voltage" (limb leads)	15	58
P waves		
Limb leads	21	96
All 12 leads*	16	90
T waves		
Limb leads	18	82
All 12 leads*	10	60

*In 18 tracings.

TABLE III. ABNORMALITIES OF RHYTHM AND CONDUCTION

	NUMBER OF CASES	PER CENT
Sinus mechanism*	22	100
Sinus bradycardia	4	18
Prolonged P-R interval	2	9
Prolonged Q-T interval	1	4

*Includes 1 with sinus arrhythmia.

RESULTS

In the 22 tracings studied, 18 contained the 12 conventional leads; the remainder included the precordial lead V_4 in addition to the 3 standard limb leads. Normal electrocardiograms were found in 3 cases, 2 of which consisted of only 4-lead tracings. Of the 12-lead tracings, 17 were abnormal.

The age at the time of bleeding, and the time when the electrocardiogram was taken are summarized in Table I. A large group of these patients were not diagnosed and did not receive treatment until 5 to 10 years after the hemorrhage that produced their illness. One of the patients was first seen 21 years following post-partum shock. Seven patients were on small doses of thyroid at the time when the electrocardiogram was taken. Five were receiving testosterone, and 2 required supplements of cortisone.

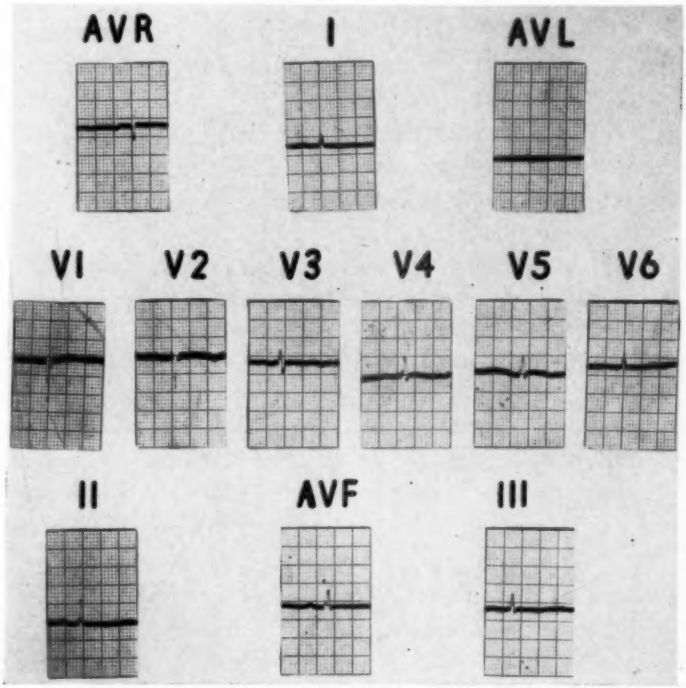


Fig. 1.—See text.

The incidence of low voltage is summarized in Table II. Because many of the tracings exhibited lower voltage than seen in most normal tracings, the term "tendency to low voltage" has been introduced to include those tracings in which the maximum amplitude of the QRS complex in the standard leads did not exceed 8 mm. (0.8 mv.). The infrequent occurrence of low voltage in the standard limb leads is of interest. It must be emphasized that approximately 60 per cent of all the tracings, however, showed at least a tendency to low voltage. In the precordial leads, low voltage was most frequent in V_5 and V_6.

Abnormal Q waves were seen in 2 cases. These included a 61-year-old woman exhibiting a small Q of 0.04 second duration in Lead III and a small

Q in aV_F, without any clinical evidence of heart disease. In another patient, 47 years old, with mild essential hypertension, there was a small Q of 0.03 second duration in Lead III, but, unfortunately, this was only a 4-lead tracing. The electrical axis was plus 60 degrees or over in about 90 per cent of the 18 cases studied.

TABLE IV. VARIATIONS IN THE P-R INTERVAL

Mean P-R interval in 20 cases (7 on thyroid therapy)	0.175 second
Mean P-R interval in 15 cases (none on therapy)	0.173 second
Mean P-R interval in normal tracings*	0.158 second

*Lown, et al.[22]

The mean P-R interval (Table IV) of 20 tracings (2 cases on cortisone therapy were omitted) was 0.175 second. There was no detectable significant difference between the treated and the untreated cases.

A fairly typical electrocardiogram is seen in Fig. 1. This patient had had a post-partum hemorrhage from retained placental parts at the age of 34 years. The tracing was taken at age 40, prior to starting replacement therapy.

DISCUSSION

Sheehan[1] in his original monogram states that the electrocardiograms (3 leads) taken "in a few cases" showed low voltage, and "findings suggestive of myxedema." Several subsequent authors[2,5] failed to specify any alterations in the electrocardiogram, except to quote from Sheehan's original work. In 1949, Sheehan and Summers[3] reviewed the tracings in 20 cases of anterior lobe hypopituitarism, including 5 cases resulting from post-partum hemorrhage. Low voltage was found in 3 tracings of the latter group, with negative T waves in Leads II and III (3-lead tracings). It was concluded that the tracings were similar to those seen in myxedema. Whittaker[14] remarked, in 9 cases, on the finding of low voltage and flattening of the T waves. Of 10 cases, Querido[15] reported low voltage in only 3, but T and S-T changes were present in 9.

Textbooks of endocrinology offer few and often vague descriptions. It is stated in one of them that the tracings are similar to those seen in Addison's disease.[16] Another finds them similar to those in hypothyroidism.[17] Nevertheless, some authors[18,19] have suggested that the electrocardiographic changes might be of help in establishing the diagnosis of anterior lobe pituitary insufficiency.

The question arises whether the electrocardiographic findings in Addison's disease and in post-partum hypopituitarism are similar. Two large series of electrocardiographic studies in Addison's disease have been reported.[20,21] The tracings were definitely abnormal in 60 and 52 per cent, respectively, of the untreated cases. In our study, approximately 90 per cent were abnormal, irrespective of therapy. The incidence of low voltage in the limb leads was approximately 15 per cent in both series of Addison's disease, and this was an infrequent finding

also in our series. Somerville and associates[21] reported low voltage in the precordial leads (V_5 or V_6) in over 35 per cent of all the cases of Addison's disease, while in our group of cases with hypopituitarism, it was about 45 per cent.

A delay in auriculoventricular conduction as measured by the P-R interval was present in 2 of our cases. This was relatively infrequent in Thorn's study[20] also, although Lown and associates[22] found heart block in 10 of 50 patients. Lown's explanation for this conduction delay in Addison's disease is that it seems to be based on fluctuations in the level of the corticosteroids which induce alterations in the metabolism of the junctional tissue at the A-V node. This effect may condition the response of the junctional tissue to sympathetic stimuli affecting the P-R interval. This conclusion appears valid since, in a large group of tracings from patients with Addison's disease, the mean P-R interval was 0.176 second. On the other hand, in a group of patients with Cushing's syndrome, with excessive secretion of cortisone-like hormones, short P-R intervals with a mean of 0.136 second was reported.[22] It must be stated that in our group with pituitary insufficiency 2 cases showed abnormal prolongation of the P-R interval. However, the mean P-R interval of the untreated cases was 0.173 second, similar to the values reported in Addison's disease.

While the Q-T interval was prolonged in about 15 per cent of the cases with Addison's disease, only 1 of our patients presented this abnormality. The tracing strongly suggested a posterior wall myocardial infarction, and the prolongation of the Q-T interval may have been related to coronary artery disease. Corticosteroids may improve the rate of ventricular repolarization in adrenal cortical insufficiency, since Somerville[21] found that the administration of cortisone shortened the Q-T interval in 6 of 12 cases of Addison's disease.

It appears as though low voltage is observed infrequently in the electrocardiograms of patients with hypopituitarism of pregnancy or Addison's disease, although prolongation of the Q-T and P-R intervals is slightly more frequent in the latter disease. The other electrocardiographic abnormalities observed in hypopituitarism of pregnancy may be related to deficiency of other pituitary factors, particularly thyroid substances.

In comparing the electrocardiograms of hypopituitarism with those of myxedema (primary hypothyroidism), certain clinical aspects must be emphasized. There is enough data to suggest that frank myxedema is not common in hypopituitarism of pregnancy.[1,23] Only rarely should the myxedematous patient confuse the clinician in respect to etiology.[24] Varying degrees of thyroid insufficiency may be encountered, depending on the severity of the post-partum pituitary necrosis. Severe hypothyroidism was not a dominant characteristic in the present series. The thyroid activity measured by the 24-hour radioiodine uptake was greater than 15 per cent in 9 of the 16 cases tested.

It appears that the electrocardiogram is generally normal in patients with mild primary hypothyroidism.[25] However, 85 per cent of those with primary myxedema show definite abnormalities.[26] Most authorities[27,28] agree with Zondek[29] that flattened P and T waves, with frequent inversion of the latter, and low voltage of the QRS complexes are the most characteristic findings.

Some authors[29] have mentioned prolongation of the P-R interval as an occasional finding, but it appears to be rare in myxedema.[26,30]

There is considerable speculation as to the cause of the low QRS voltage in myxedema, but it does not appear to be related to poor conductivity of the skin.[31] Perhaps this low voltage may be governed by the weak action potential generated in the edematous myocardial tissue,[32,33] or by pericardial effusion. Kern[34] has demonstrated significant pericardial effusions in 4 patients with primary myxedema. The electrocardiographic changes, which included low QRS voltage, were partially reversed immediately after pericardial paracentesis. Marks and Roof[33] maintain that pericardial effusion is an important factor in the production of the abnormal electrocardiographic tracings. Pericardial effusion was found in only 2 of 20 cases of primary myxedema studied in Puerto Rico[35]; however, not all were submitted to pericardial taps. Clinically significant pericardial effusion was not detected in any of the cases of hypopituitarism of pregnancy. Posteroanterior roentgenographic studies in the 22 cases failed to reveal cardiac enlargement, in contrast to the observations of Kern[34] and Marks[33] in myxedema. Some of the hypopituitary patients showed small vertical hearts, similar to those described in Addison's disease.[20] This finding correlates well with the electrocardiographic finding of an electrical axis of 60 degrees or more in the great majority of our cases. Of 24 cases with primary myxedema, reported by Lerman,[26] 7 showed left axis deviation. It must be emphasized that none of our cases showed left axis deviation. Sinus bradycardia, so commonly observed in primary myxedema, was an infrequent finding in our series.

Presumably, the presence of small, flattened, or inverted T waves in 18 of our cases may be attributed to the thyroid or, perhaps, to the adrenal cortical insufficiency. In a recent vectorcardiographic study of primary hypothyroidism, it was concluded that the alterations in the T waves appeared to be related to the altered cellular metabolism which apparently retards the process of repolarization of the ventricles.[36] Whether the T-wave changes frequently observed in Addison's disease are related to the accompanying depression of the metabolic rate remains unanswered.

The majority of the electrocardiograms of patients with pituitary insufficiency and primary myxedema exhibit nonspecific T-wave changes, probably related, in part, to thyroid deficiency. In both, low amplitude of the P and T waves are frequent, but low voltage of the QRS complex is uncommon in the pituitary group, although a tendency to low voltage was present in the majority. Left axis deviation, seen in about one third of patients with primary myxedema, is rare in hypopituitarism of pregnancy. Neither disease is associated with abnormal prolongation of the P-R interval.

Whether insufficiency of the anterior lobe of the pituitary predisposes to coronary artery disease remains unanswered, although some investigators have mentioned the possibility of a causal relationship.[3,37] A follow-up study of our 22 patients, for as long as 25 years, has failed to uncover clinical evidence of cardiac insufficiency. Only 2 patients showed evidence of vascular disease; one had mild hypertension, and the other, probable electrocardiographic signs of coronary artery disease.

It seems that oral daily doses of ½ to 1 grain of desiccated thryoid failed to alter the electrical activity of the heart, as determined by the electrocardiogram in 12 patients. In 5 of these patients, serial electrocardiograms before and after the institution of therapy showed no significant alterations in the heart rate, amplitude of the QRS complexes, or the P and T waves. The duration of this therapy was between 2 and 15 months. When cortisone was administered in conjunction with thyroid, the P-R interval was shortened in the one instance tested.

The administration of cortisone with larger doses of thyroid (2 to 3 grains daily) has been reported to improve the electrocardiographic picture of hypopituitarism.[6] Contrary to the dramatic clinical improvement that follows thyroid therapy in primary hypothyroidism, the response of pituitary hypothyroidism is inadequate if unaccompanied by steroid therapy.

SUMMARY

Nineteen of 22 patients with well-documented hypopituitarism of pregnancy showed definite electrocardiographic changes. Seventeen with 12-lead tracings were abnormal. Small, flattened or inverted T waves were generally seen, together with small P waves in the majority of the leads. Low voltage of the QRS complexes was uncommon. Left axis deviation was rare. Prolongation of the Q-T interval and first degree heart block also were unusual, although the mean P-R interval was slightly prolonged. The oral administration of thryoid in small doses did not significantly alter the electrocardiogram.

Because depression of the functions of the anterior lobe of the pituitary is not uniform following post-partum necrosis, there are variations in the target organ response. The electrocardiogram seems to reflect these changes. However, they do not appear to be diagnostic of any particular hormonal deficiency, and some of these abnormalities are seen with varying frequency in Addison's disease and primary myxedema.

In the patient with a history of post-partum or intrapregnancy hemorrhage, and the clinical picture of insufficiency of the anterior lobe of the pituitary, the electrocardiographic changes described should be expected.

The authors wish to acknowledge the helpful criticism of Drs. R. S. Diaz-Rivera and Manuel Torres-Gomez, and the cooperation of the Cardiac Clinic, San Juan City Hospital, under the direction of Dr. F. Diez-Rivas.

REFERENCES

1. Sheehan, H. L.: Quart. J. Med. **8**:277, 1939.
2. Escamilla, R. F., and Lisser, H.: J. Clin. Endocrinol. **2**:65, 1942.
3. Sheehan, H. L., and Summers, V. K.: Quart. J. Med. **18**:319, 1949.
4. Sheehan, H. L.: Am. J. Obst. & Gynec. **68**:202, 1954.
5. Perkins, R. F., and Rynearson, E. H.: J. Clin. Endocrinol. **12**:574, 1952.
6. Beck, R. N., and Montgomery, D. A. D.: Brit. M. J. **1**:441, 1957.
7. Sheehan, H. L., and Summers, V. K.: Brit. M. J. **1**:723, 1954.
8. de Andino, A. M., Jr.: Unpublished data.
9. Burch, G. E., and Winsor, T.: A Primer of Electrocardiography, Ed. 3, Philadelphia, 1955, Lea & Febiger.
10. Katz, L. N.: Electrocardiography, Philadelphia, 1946, Lea & Febiger.

11. Lapin, A. W.: Am. Heart J. **33**:747, 1947.
12. Ashman, R., and Hull, E.: Essentials of Electrocardiography, Ed. 2, New York, 1945, The Macmillan Company.
13. Goldberger, E.: Unipolar Lead Electrocardiography and Vectorcardiography, Ed. 3, Philadelphia 1953, Lea & Febiger.
14. Whittaker, S. R. F., and Whitehead, T. P.: Brit. M. J. **2**:265, 1954.
15. Querido, A., van der Werfften-Bosch, J. J., Blon, P. S., and Van Gilse, H. A.: Acta med. scandinav. **149**:291, 1954.
16. Spence, A. W.: Clinical Endocrinology, London, 1953, Cassell and Company.
17. Soffer, L. J.: Diseases of the Endocrine Glands, Philadelphia, 1951, Lea & Febiger.
18. Evans, W.: Proc. Roy. Soc. Med. **42**:331, 1949.
19. Heyde, E. C.: A.M.A. Arch. Int. Med. **92**:442, 1953.
20. Thorn, G. W., Dorrance, S. S., and Day, E.: Ann. Int. Med. **16**:1053, 1942.
21. Somerville, W., Levine, H. D., and Thorn, G. W.: Medicine **30**:43, 1951.
22. Lown, B., Arons, W. L., Ganong, W. F., Vazifdar, J. P., and Levine, S. A.: Am. Heart J. **50**:760, 1955.
23. Cluxton, H. E., Bennett, W. A., and Kepler, E. J.: Ann. Int. Med. **29**:732, 1948.
24. Means, J. H., Hertz, S., and Lerman, J.: Tr. A. Am. Physicians **55**:32, 1940.
25. Reid, W. D., and Kenway, F. L.: Endocrinology **13**:191, 1929.
26. Lerman, J., Clark, R. J., and Means, J. H.: Ann. Int. Med. **6**:1251, 1933.
27. Selye, H.: Textbook of Endocrinology, Montreal, 1947, Acta Endocrinologia, Université de Montreal.
28. White, P. D.: Heart Disease, Ed. 4, New York, 1951, The Macmillan Company.
29. Zondek, H.: Lancet **2**:310, 1941.
30. Thacher, C., and White, P. D.: Am. J. M. Sc. **171**:61, 1926.
31. Fournier, J. C. M.: Proc. Staff Meet. Mayo Clinic **17**:212, 1942.
32. Friedberg, C. K.: Diseases of the Heart, Ed. 2, Philadelphia, 1956, W. B. Saunders Company.
33. Marks, P. A., and Roof, B. S.: Ann Int. Med. **39**:230, 1953.
34. Kern, R. A., Soloff, L. A., Snape, W. J., and Bello, C. T.: Am. J. M. Sc. **217**:609, 1949.
35. de Andino, A. M., Jr., and Rodriguez, R.: Bol. Asoc. méd. Puerto Rico. (Submitted for publication.)
36. Urschel, D. L., and Gates, G. E.: Am. Heart J. **45**:611, 1953.
37. Wilson, L. A.: Lancet **1**:203, 1953.

Experimental Heart Failure in Rabbits With Hypertension

Alfredo Franco, M.D., Lisbon, Portugal

In spite of their number, the tests made for the production of experimental cardiac insufficiency have not produced very satisfactory results. Various methods have been adopted for the production of experimental cardiac insufficiency. Coelho and Rocheta[1] produced edema of the lung by injecting nitrate of silver into the wall of the left ventricle. Cataldi[2] repeated these experiments and verified that pulmonary edema appeared equally when the toxic substance was injected into the right ventricle, the ventricular fibrillation resulting even less often than is frequently observed when the necrosis is localized in the left ventricle. Ligature of the coronary arteries, used by Coelho and Rocheta[3] and Orias,[4] did not give the desired effects, although at times signs of heart failure occurred. Armstrong[5] observed predominately right cardiac insufficiency by intrapericardial injection of Dakin's solution and iodine. Boucek, Grindlay and Burchell[6] describe the appearance of circulatory insufficiency in the dog, by constriction of the right and left inflow tracts. Drury and Wightman[7] produced hypertrophy and cardiac dilatation by anastomosing the right carotid to the external jugular vein. Roos and Smith[8] produced congestive heart failure in the dog by injecting into the left ventricle a suspension of starch particles in physiologic saline, closing the aorta during the injection. Barger, Roe and Richardson[9] verified that a combination of tricuspid insufficiency and pulmonary stenosis would determine a syndrome similar to right chronic congestive insufficiency. Davis, Hyatt and Howell[10] produced right cardiac insufficiency by progressive constriction of the pulmonary artery in the dog. Alexander, Edmondson and Drury[11] observed, in the rabbit, the development of hypertensive heart failure by constriction of the abdominal aorta. Porto[12-14] has determined with facility acute edema of the lung by injecting intravenously a toxic substance (nitrate of silver) into the thickness of either of the ventricles, by the aorta or into the actual ventricular cavities.

The manifestations of heart failure that are obtained by the processes described are, in general, limited and the methods that provoke them are singularly removed from the states that in human pathology usually give rise to them. However, the experimental production of a situation, such as hypertension, that

From the Laboratory of Experimental Cardiology Anibal de Castro, Hospitais Civis de Lisboa.
Received for publication Aug. 5, 1957.

leads frequently to congestive cardiac insufficiency in man should, in principle, produce the same results in the animal. Besides this, it is logical, on the other hand, to expect that experimental hypertension will approximate more nearly the hypertensive illness of man if it is developed in animals whose vascular systems present atherosclerotic lesions. Wakerlin and co-workers,[15] studying the effect of experimental hypertension on experimental cholesterol atherosclerosis, suggest the possibility of the production of experimental chronic myocardial insufficiency.

In the course of experimental study of the interrelations between hypertension and atherosclerosis, we can verify, in fact, the development of congestive cardiac insufficiency not only in animals in which, besides hypertension, vascular atheromatous lesions were provoked, but even in those in which only hypertension was produced. The results which were observed are described below.

METHOD

We used the rabbit as an experimental animal. The hypertension was provoked by the method described by Pickering and Prinzmetal,[16] and the vascular lesions by the daily administration of 1.5 Gm. of cholesterol. The animals were divided into 3 groups (Table I): Group P-A—In this group only hypertension was produced. Group P-B—To these animals cholesterol was given in addition to the production of hypertension. Group CLT—Only cholesterol was administered to this group, without hypertension being provoked.

The arterial pressure was measured in the central artery of the ear by means of the capsule of Grant and Rothschild,[17] according to the method described by Pickering. Electrocardiograms, x-rays of the thorax, and analysis of urine and urea of the blood were obtained regularly. None of the animals was sacrificed, death in each case being spontaneous.

RESULTS

In most of the animals pressure reached a figure between 95 and 130 mm. Hg—110/130 in those which had developed signs of cardiac insufficiency (Table II). Initial blood pressure was 45/60 mm. Hg. In several cases and with greater frequency in Group P-B, signs of cardiac insufficiency were produced, reproducing at times the changes that are habitually found in human hypertensive cardiopathy. Characteristics presented by the 3 groups of animals are given below.

GROUP P-A

The survival time of the animals with evidence of cardiac insufficiency (4 out of 8) was, on the average, 73 days after the placing of the clamp in the left renal artery. The blood pressure of the same 4 animals varied between 110 and 125 mm. Hg. Reduction of weight (an average of 600 grams) was always noticed.

Autopsy.—Subcutaneous tissue was diffusely infiltrated by a clear liquid that flowed when the tissue was cut. In all the serous cavities there existed small effusions, clear and colorless, being more predominant in the pleural cavities. The heart was hypertrophied, principally the left ventricle. Neither in the endocardium nor in the intima of the great vessels were alterations observed. The lungs were heavy, with little air, and, when they were cut, a clear slightly rose-colored liquid mixed with air flowed from the surface of the section. The liver was increased in size and red in color, with a noticeable and well-marked lobulation on the surface of the section.

Kidneys and spleen were red in color. The suprarenals were small and normal in color. The remaining (left) kidney was systematically increased in size. Average weight of the heart was 8.6 grams, with the increase fundamentally in the left ventricle.

TABLE I

	NUMBER OF ANIMALS	NUMBER OF ANIMALS WITH SIGNS OF CARDIAC INSUFFICIENCY
P-A	8	4
P-B	8	6
CLT	10	0

TABLE II. PERIOD OF SURVIVAL AND BLOOD PRESSURE IN THE ANIMALS WITH SIGNS OF CARDIAC INSUFFICIENCY

GROUP	RABBIT	PERIOD OF SURVIVAL (DAYS)	FINAL BLOOD PRESSURE (MM. Hg)
P-A	17	67	120
	30	70	125
	4	81	115
	13	75	110
P-B	1	159	125
	7	184	115
	8	153	120
	11	165	115
	12	176	130
	15	163	120

Microscopic Examination.—

Heart: The muscular cardiac fiber, compared with that of a set of normal rabbits of identical weight, appeared increased. No other myocardial alterations were found, especially foci of fibrosis.

Coronary arteries: It was noted that several of the coronary arteries, compared with vessels as identical as possible in normal rabbits with the same weight, showed a thicker wall, due apparently to an increase in the number of layers of smooth muscular fibers and to the individual increase of each fiber: consequently, the lumen was narrower and not infrequently was observed in some cases to be reduced to a crack, although there were no alterations of the intima. These alterations were less in the smaller arteries (Fig. 1).

Lungs: The general structure of the lungs was preserved, but the alveoli were reduced in size because of thickening of the interalveolar septa. This thickening was made through an increase in the number of the cells, both fixed cells and histiocytes. Eosinophils were found also in great numbers. The alveolar cavities had a fair number of desquamated cells and erythrocytes. These cells were of the type of the big alveolar cells, and the cytoplasm was loaded with hemosiderin.

In the regions in which this cellular density was greatest, the alveolar structure was hardly recognized. In sections stained with Van Gieson it was verified that in the thickening of these septa there was practically no participation of collagen. At several points were found groups of alveoli full of plasma, with few or no cells; the same plasma was found also, but in lesser quantity, in alveoli with a goodly number of cells. Almost all the capillaries were dilated and many of them distended with blood. In several small bronchi there existed masses of hemosiderophagi (Fig. 2).

Fig. 1.

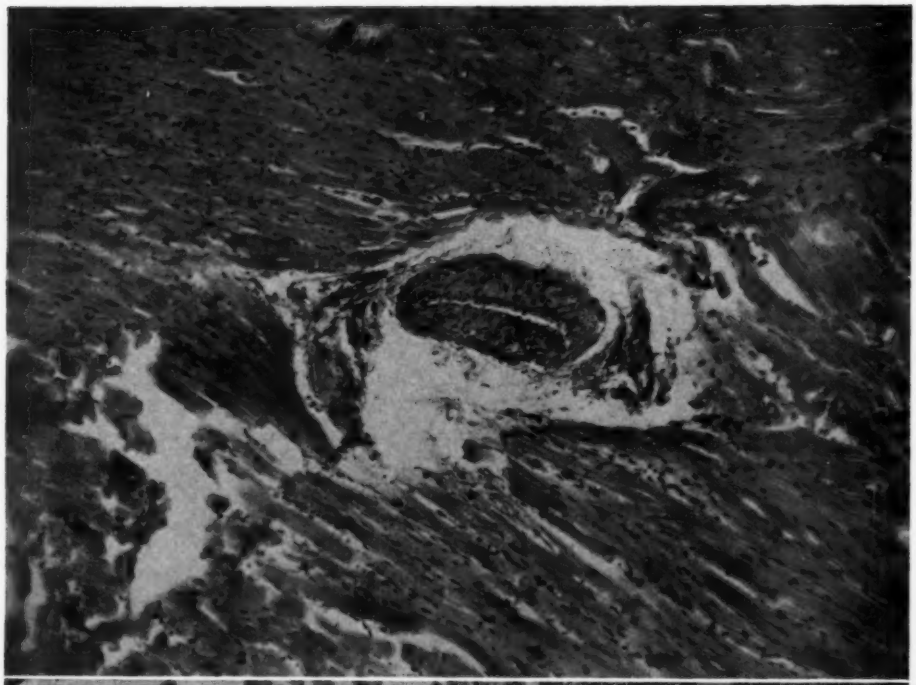


Fig. 2.

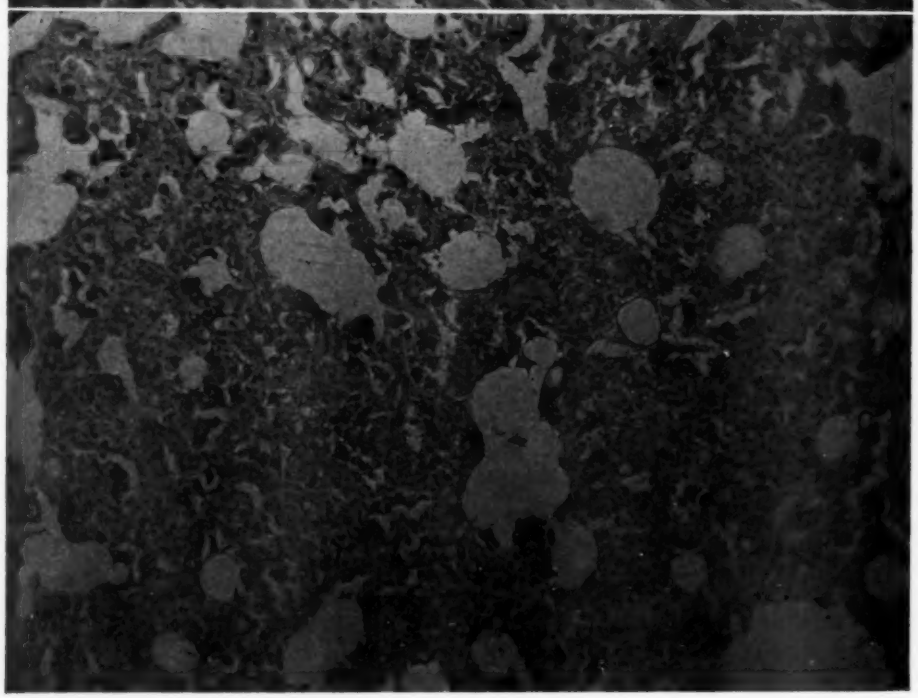


Fig. 1.—Rabbit of Group P-A. Myocardium: marked narrowing of the lumen of one artery with hypertrophy of the media (hematoxylin-eosin).
Fig. 2.—Rabbit of Group P-A. Lung: alveoli containing many hemosiderophagi (Perl's).

Liver: The liver of the animals of this group presented alterations of almost all the lobules, in the sense of a blood stasis: the centrolobular veins were very much dilated, as were also the intertrabecular capillaries. The trabeculae of Remak were atrophied in the central zones of the lobe and their cells were frequently loose, with cellular limits not clearly defined and often with necrosis. In the zones of greater stasis, cellular remains were observed, mixed with blood, and the central veins no longer had precise limits. Many of the suprahepatic veins were very much dilated. In none of the cases was fibrosis observed. These alterations were more marked in some cases than in others (Fig. 3).

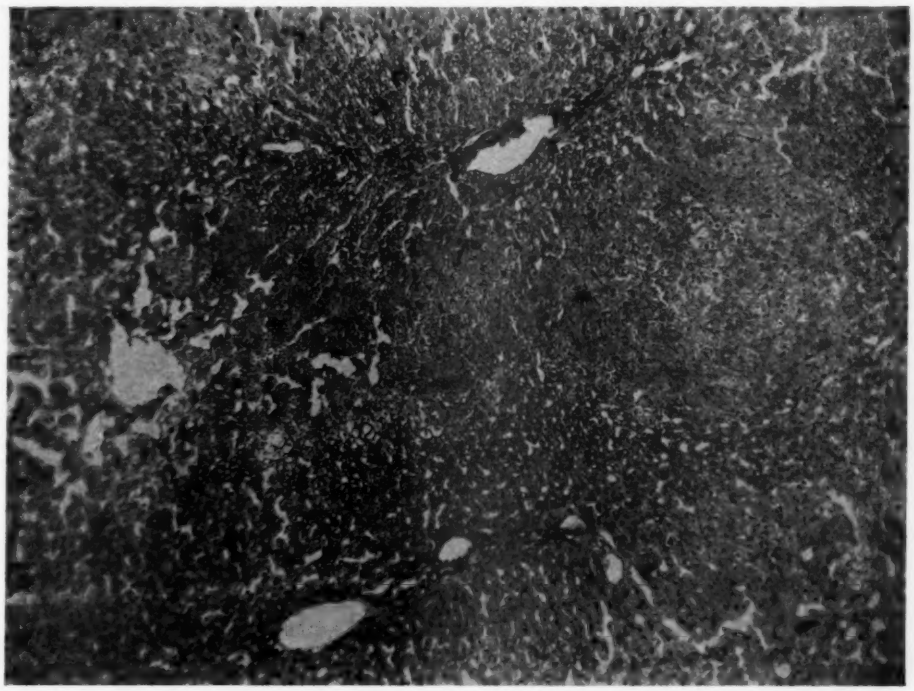


Fig. 3.—Rabbit of Group P-A. Liver stasis, with necrosis of the central hepatic cells (hematoxylin-eosin).

Spleen: The pulp was red and rich in blood, with the splenic sinuses very much dilated—at times almost cavernous—and the parenchymatous cords fine and with few cells. With Perl's stain an exaggerated quantity of hemosiderin in relation to the normal was observed. The lymphatic follicles did not show alterations and were found well delimited in the middle of the red pulp. The walls of the small arteries near and within the lymphatic follicles showed a thick muscular layer, which corresponded to hypertrophy when compared with identical vessels of normal rabbits.

Kidney: There were dilatations of the small vessels of the medulla, with the lumen full of blood. There were no alterations in the uriniferous collector canals of the vicinity. In the cortex were found several dilated capillaries, but not so many as in the medulla. Also, the glomeruli contained erythrocytes in the capillary loops in a slightly increased number, without other alterations. In certain of the glomeruli Bowman's space was found to contain plasma.

GROUP P-B

The survival time of the animals with signs of cardiac insufficiency (6 out of 8) was, on the average, 166 days after the placing of the clamp. The blood

Fig. 4.

Fig. 5.

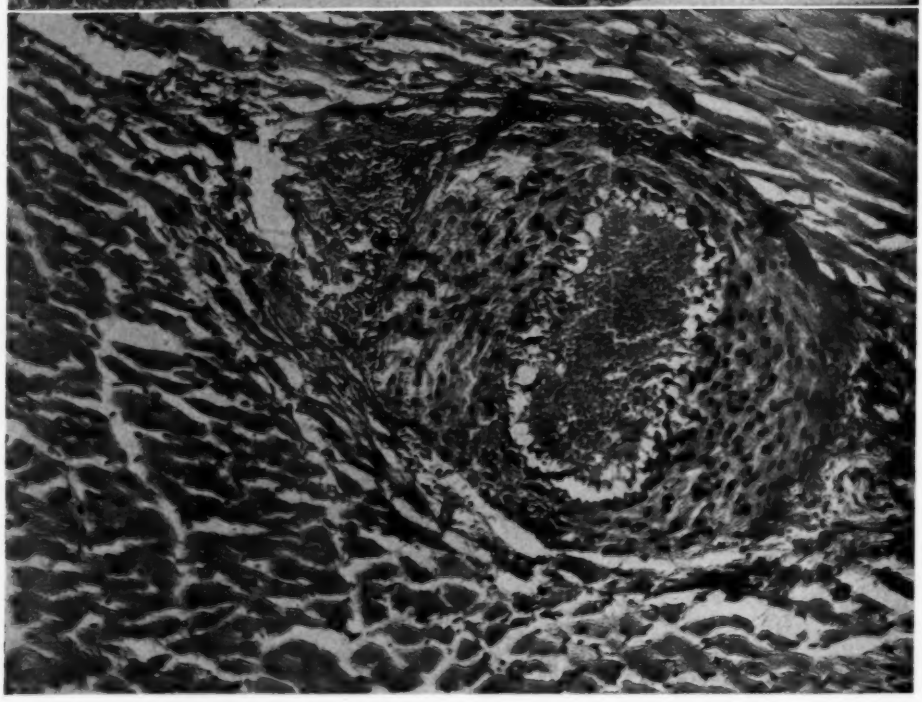


Fig. 4.—Rabbit of Group P-B. Heart: small coronary subendocardiac branch with large fibrous cushion. Fibrosis of the myocardium (hematoxylin-eosin).

Fig. 5.—Rabbit of Group P-B. Coronary branch with marked hypertrophy of the media (hematoxylin-eosin).

Fig. 6.

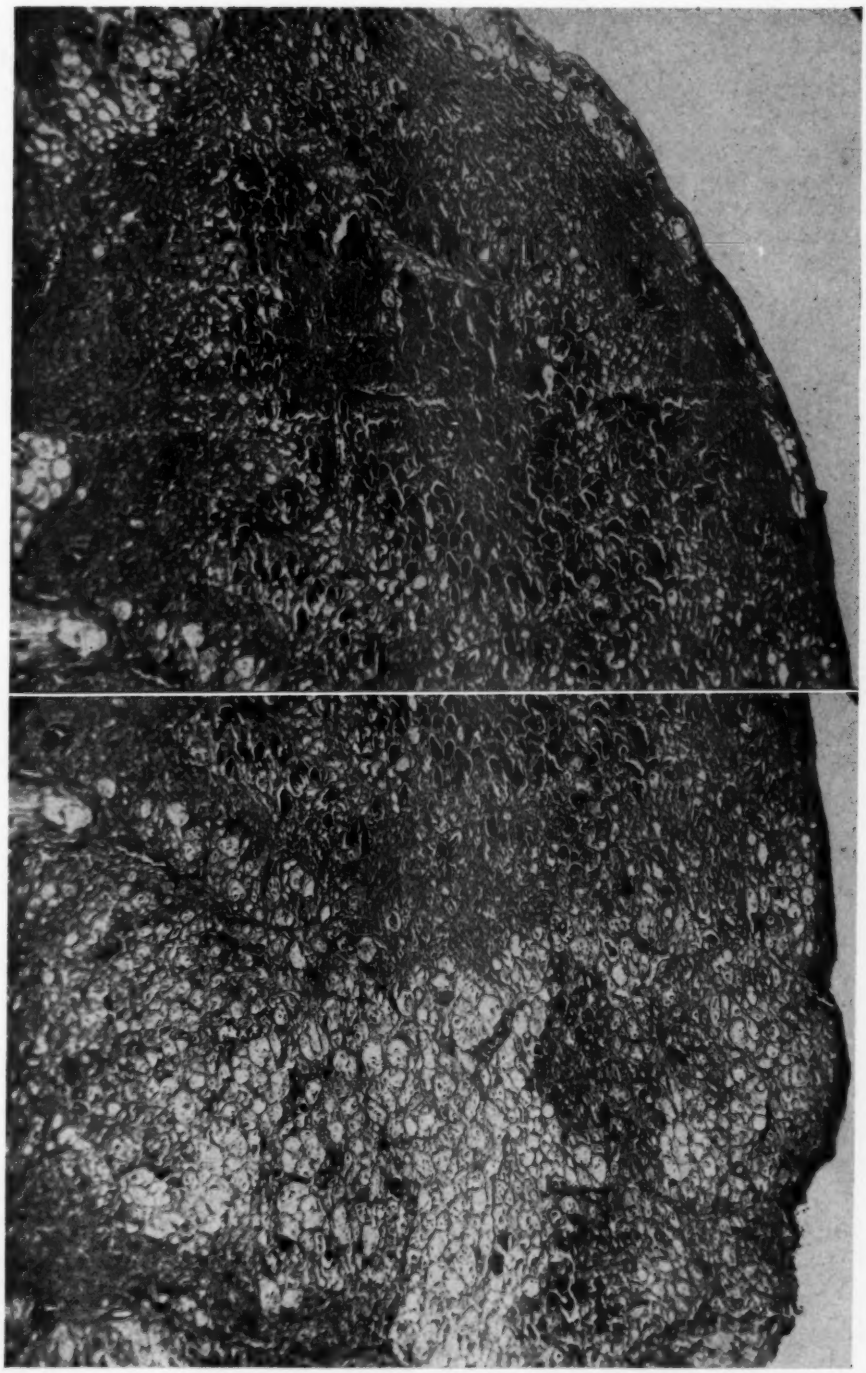


Fig. 7.

Fig. 6.—Rabbit of Group P-B. Heart: very intense fibrosis of the base of a papillary muscle of the left ventricle (Mallory).

Fig. 7.—Rabbit of Group P-B. Heart: vacuolization of the muscular fibers (Mallory).

pressure of the same 6 animals varied between 115 and 130 mm. Hg. At the time of death, which was always spontaneous, they showed an average loss of weight of 530 grams.

Autopsy.—Lesions of the intima in the form of salient yellow foci were found principally in the aorta. In the most serious forms there was a larger number of these yellow foci of greater dimensions, joining together at times in large zones of the intima. In the most marked cases these deposits gave an unequal and irregular relief to the intima of the vessel. They were more numerous in the ascendant aorta and in the arch, diminishing afterward in number and size, being almost nonexistent in the abdominal aorta. The liver was greater than that of a normal rabbit, and of

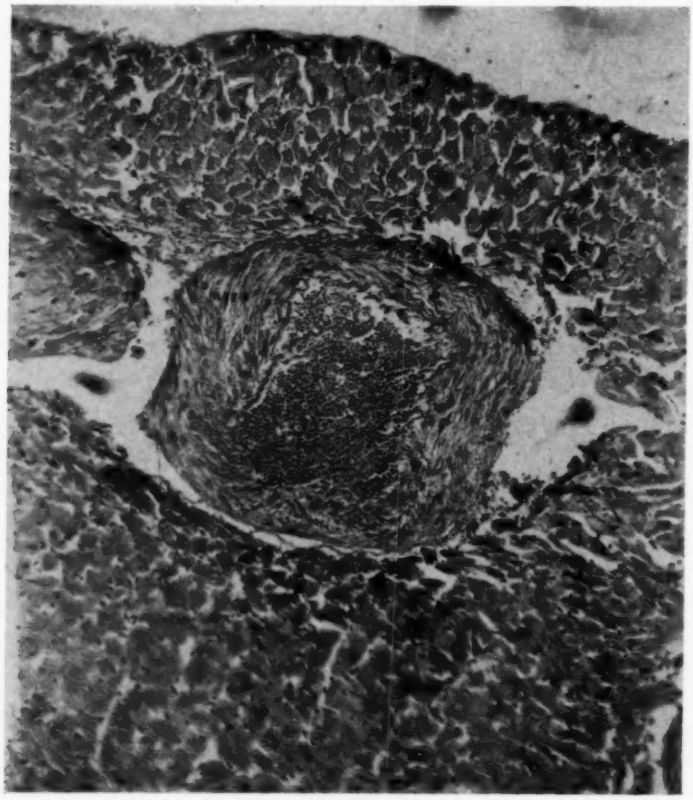


Fig. 8.—Rabbit of Group P-B. Heart: coronary branch of the left ventricle with hypertrophy of the media (hematoxylin-eosin).

a pronounced yellow color, with the lobulation well marked. The spleen was large, in some instances 3 to 4 times greater than the normal, and of a grayish-yellow color. Beneath the capsule were distinct yellow foci, more active, and pin point in size. Suprarenals were systematically increased in size and of a pronounced yellow color. The lungs were rich in frothy liquid. In 2 animals the kidneys were surrounded by a thick coating of a yellow substance of the consistency of mush. The heart was hypertrophied, chiefly the left ventricle. The remaining (left) kidney was large. The average weight of the heart was 10.95 grams, reaching 17 grams in 1 case.

Microscopic Examination.—

Heart: A great part of the coronary branches of greater and medium caliber showed the wall clearly thickened by the increase in the volume of the smooth muscle fibers. In the vessels of smaller caliber there were found deposits of lipid, with widening of the intima by accumulation of foam cells, and consequent reduction, almost always very intense, of the lumen.

Fig. 9.

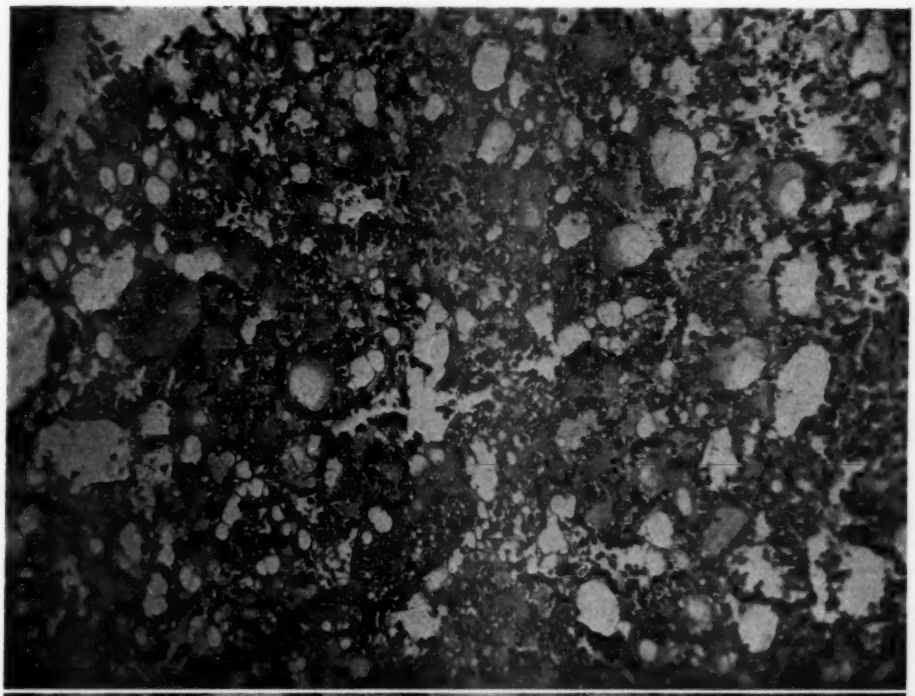


Fig. 10.

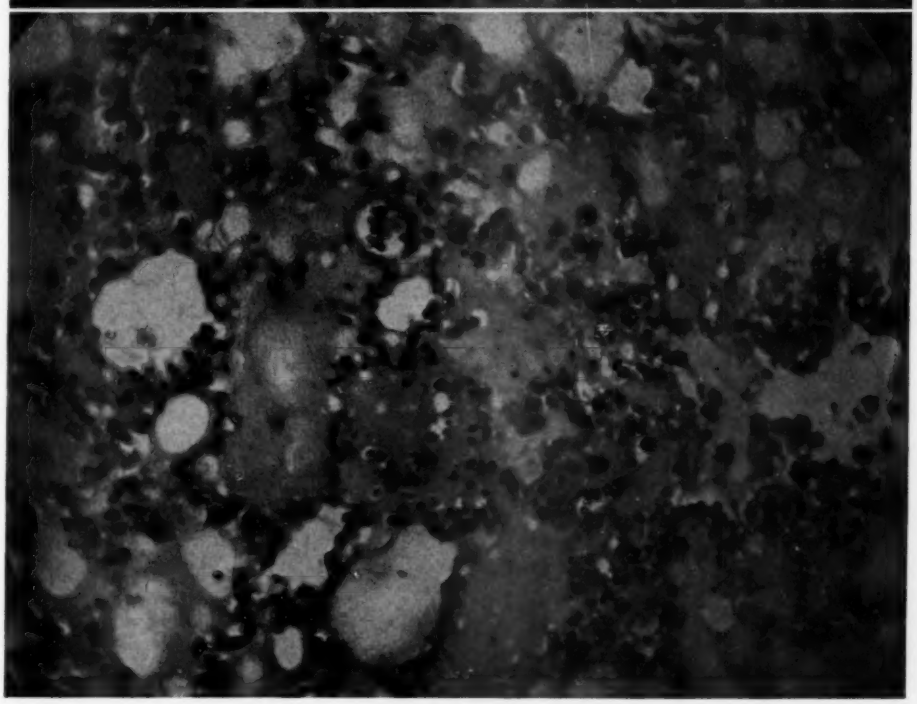


Fig. 9.—Rabbit of Group P-B. Lung: intra-alveolar edema. (Small amplification. Hematoxylin-eosin stain.)

Fig. 10.—Same as Fig. 9, with greater amplification.

Fig. 11.

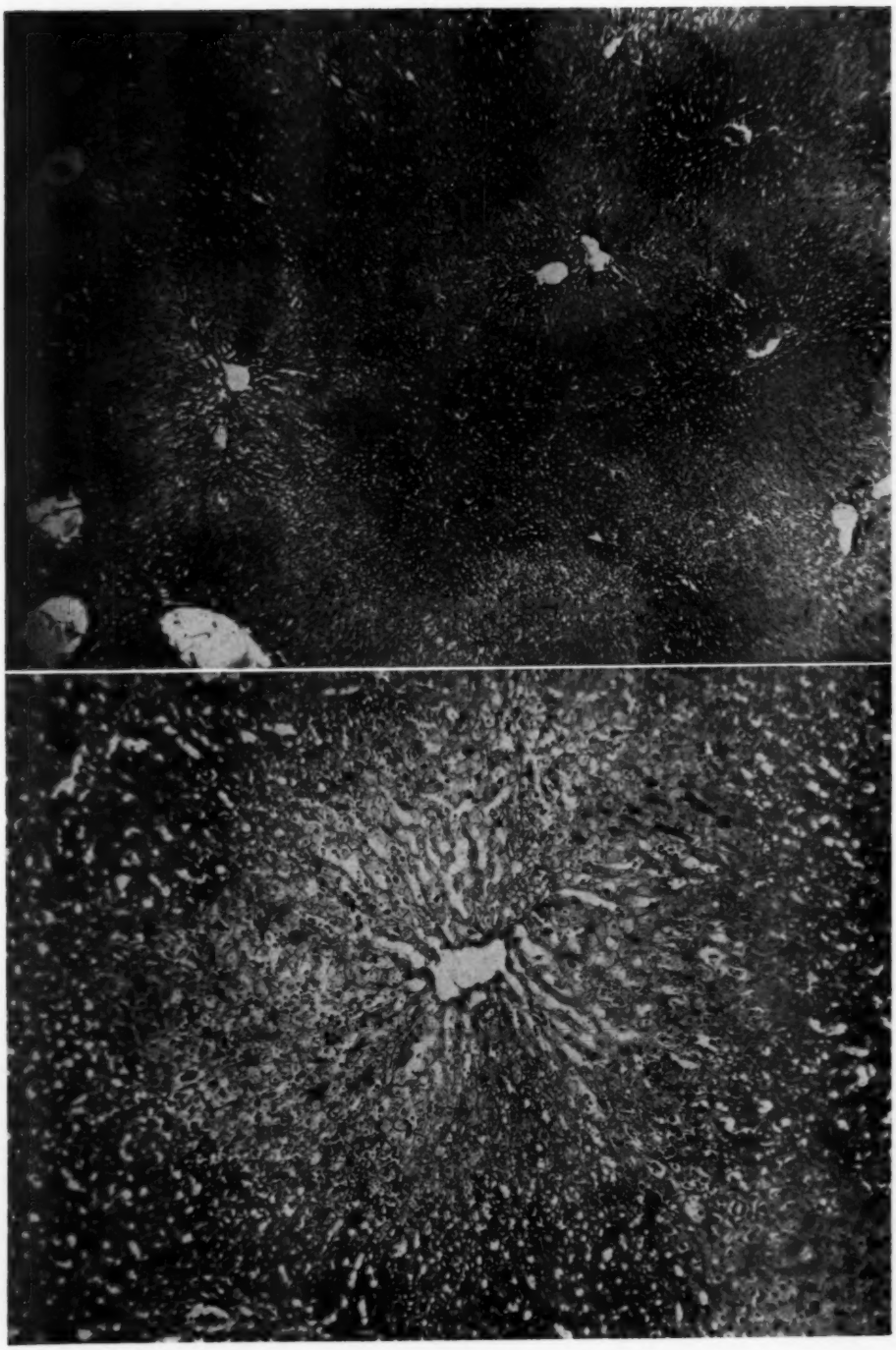
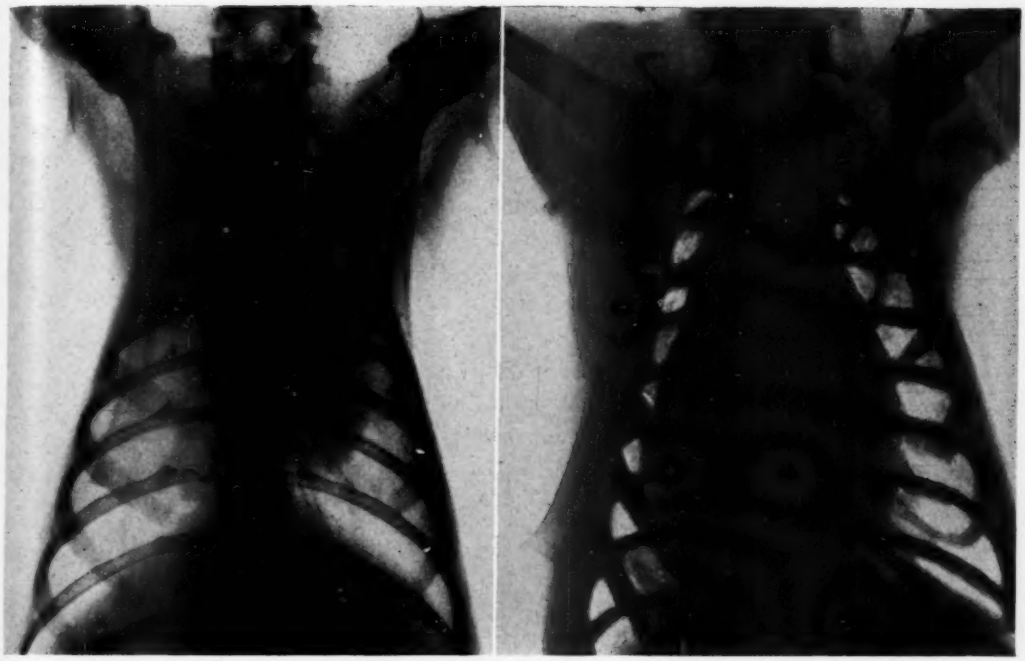


Fig. 12.

Fig. 11.—Rabbit of Group P-B. Liver stasis (Lupa's hematoxylin-eosin).
Fig. 12.—Same as Fig. 11, slightly amplified (hematoxylin-eosin).



A. *B.*

Fig. 13.—*A*, Cardiac silhouette of a normal rabbit. *B*, Enlarged heart of rabbit with hypertension and atherosclerosis (Group P-B).

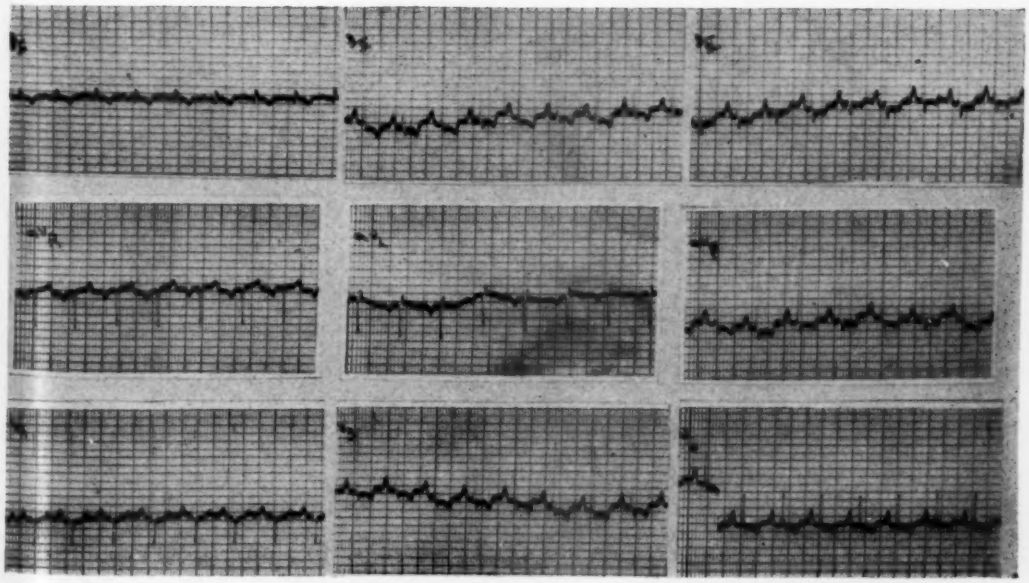


Fig. 14.—Rabbit of Group P-B. Hypertrophy and left ventricular strain. (Am. Heart J. 54:69, 1957.)

Compared to the animals of Group P-A, the hypertrophy of the vascular walls was more intense, extending to the greater vessels. At the level of the wall of the right ventricle, arterial branches with this hypertrophy were found, which was not observed in the other groups of animals. Extensive zones of fibrosis were found, with atrophy and disappearance of the muscular cardiac fibers in these fields. In 1 heart, a zone of necrosis of muscular fibers was even observed, with chromatolysis very much accentuated at the level of a papillary muscle. The zones of fibrosis were very extensive, and at the level of which the total disappearance of the muscular fields was observed. These foci were localized chiefly in the subendocardiac zones (Figs. 4 through 8).

Lungs: In each case of this group, the common characteristic found was that a great part of the alveoli contained plasma, alone or with a small quantity of cells. Among the cells were to be found several polynuclear ones, and principally macrophagi. There were many extravasated erythrocytes, either in the septa or within the alveoli. The septa, as a rule, were narrow and their capillaries moderately dilated. The dominant character was that of intra-alveolar plasma (Figs. 9 and 10).

Liver: There was a very intense infiltration of lipoid in the hepatic cells, which were increased in size and had vacuolized cytoplasm. Alterations of the type of those of the blood stasis verified in Group P-A were noted, although less marked (Figs. 11 and 12).

Spleen: There were dilatations of the sinusal spaces with atrophy of the cords, as in Group P-A, but less marked. Proliferation of the reticular elements, transformed into lipophagi, were noted. The quantity of hemosiderin was normal, or slightly increased. In some cases, walls of the fine arterial branches showed muscular hypertrophy, although of a more reduced grade and fewer in number than in the spleens of Group P-A.

Kidney: The common characteristic in the kidney was the lipoid in cells whose cytoplasma had a foamy aspect, whether of the epithelium of the uriniferous tubes, the glomerular endothelium, or the elements of the conjunctive interstitial tissue. In some cases, "cushions" of these cells were found in the intima of the renal vessels, frequently with intense fibrous reaction and reduction of the vascular caliber. In 2 there was an intense accumulation of foam cells outside the renal capsule, along a large extension of the kidney, with the formation of a second fibrous capsule outside this accumulation.

The interstitial accumulation of foam cells in the Bellini tubes was the fundamental abnormality of some kidneys, with many crystals of cholesterine and reaction of a foreign body. There was blood stasis in certain cases.

GROUP CLT

The alterations that were found in the animals of this group were in relation to the administration of cholesterol and were described in a previous work.[18] In no case were signs of heart failure found.

COMMENTS

The descriptions given correspond to states of congestive cardiac insufficiency occurring in hypertensive animals. Thus it was shown that the experimental hypertension of the rabbit, produced by the method of Pickering and Prinzmetal, can produce a hypertensive cardiopathy, reproducing in a more or less complete form the degrees that are habitually found in the human disease.

It is likewise demonstrated that the gravity of hypertension, in the non-malignant forms, does not come solely from the lesions of atherosclerosis that may possibly exist.

The laboratory examinations are equally similar to those observed in man.

In the urine, albuminuria was found, ranging from marked traces to, in one case, 1.5 per cent, leukocytes, erythrocytes, hyaline, granular and epithelial casts. Often there was found to be an increase of urea in the blood, in general

from 0.80 to 1.60 per cent. In one case of Group P-A, 4.70 per cent was found on the day of the animal's death. Radiologically, an enlargement of the volume of the heart (Fig. 13, *A* and *B*) was noted. Electrocardiographically, traces of hypertrophy and left ventricular strain were registered[19] (Fig. 14).

In experimental hypertension, the conditions we have described are not always developed. In order to produce them it is necessary to have an "optimal" opening of the arms of the clamp: neither so tight that it results in a malignant hypertension[20] nor so loose that it gives rise to a favorable hypertension of long duration. In general, we used clamps whose opening was from 0.4 to 0.5 mm. In the animals of Group P-B, signs of congestive insufficiency were produced in a greater number of cases. The fact is due possibly to (1) the development of atheromatous lesions that would determine a certain reduction of the arterial renal lumen, or (2) the alterations of the fibrosis produced at the level of the myocardium, which should contribute to its failure.

SUMMARY

The manifestations of congestive cardiac insufficiency are described, as observed in one group of rabbits in which experimental hypertension was produced by the method of Pickering and Prinzmetal, and in another group in which, in addition to hypertension, vascular atheromatous lesions were provoked by the administration of cholesterol.

I should like to express my deep appreciation to Professor Pickering for his valuable guidance.

REFERENCES

1. Coelho, E., and Rocheta, J.: Ann. de méd. **34**:91, 1933.
2. Cataldi, G. M.: Arch. mal. coeur **28**:604, 1935.
3. Coelho, E., and Rocheta, J.: Compt. rend. Soc. de biol. **102**:203, 1929.
4. Orias, O.: Am. J. Physiol. **100**:629, 1932.
5. Armstrong, T. G.: Quart. J. Exper. Physiol. **30**:263, 1940.
6. Boucek, R. J., Grindlay, J. H., and Burchell, H. B.: Am. J. Physiol. **169**:434, 1952.
7. Drury, A. N., and Wightman, K. J. R.: Quart. J. Exper. Physiol. **30**:45, 1940.
8. Roos, A., and Smith, J. R.: Am. J. Physiol. **153**:558, 1948.
9. Barger, A. C., Roe, B. B., and Richardson, G. S.: Am. J. Physiol. **169**:384, 1952.
10. Davis, J. O., Hyatt, R. E., and Howell, D. S.: Circulation Res. **3**:252, 1955.
11. Alexander, N., Edmondson, H. A., and Drury, D. R.: Circulation Res. 1:491, 1953.
12. Porto, J.: Edema agudo de pulmón y circulación de reflujo, Madrid, 1950, Imprenta de J. Cosano.
13. Porto, J.: Jornal do Médico **18**:5, 1951.
14. Porto, J., and Robalo, C.: Cardiologia **21**:420, 1952.
15. Wakerlin, G. E., Moss, W. G., Neville, J. B., and Bourque, J. E.: Effect of Experimental Renal Hypertension on Experimental Cholesterol Atherosclerosis. Fifth Conference on Factors Regulating Blood Pressure, New York, 1951, Josiah Macy, Jr., Foundation.
16. Pickering, G. W., and Prinzmetal, M.: Clin. Sc. **3**:357, 1938.
17. Grant, R. T., and Rothschild, P.: J. Physiol. **81**:265, 1934.
18. Franco, A.: Aterosclerose clinica a experimental. Actas do II Congresso Luso-Espanhol de Cardiologia, Lisboa, 1956.
19. Franco, A.: Am. Heart J. **54**:69, 1957.
20. Wilson, C., and Pickering, G. W.: Clin. Sc. **3**:343, 1938.

Wandering Liver and Tachycardia

R. R. Grayson, M.D., Perryville, Mo.

This report is prompted by a patient whom we treated recently for right upper quadrant pain and liver enlargement which was apparent only when the patient was erect. Despite exhaustive studies and consultations the true nature of the disease in this patient was not discovered until an exploratory laparotomy had been performed.

A partial review of the literature and of recent textbooks reveals few references to this subject. It is my impression that most physicians are unaware of the possibility of hepatoptosis and do not include this condition in their differential diagnosis of right upper quadrant liver enlargement and pain.

A profound discussion of hepatoptosis is found in the *Index of Differential Diagnosis* by French.[1] The description given by French is so well done that I do not feel I could improve upon it by paraphrasing him. He states:

> *Hepatoptosis* and *wandering liver* are terms applied to a liver which leaves its normal position. A liver which is only displaced may erroneously be thought to be enlarged. Extreme degrees are met with in cases of general visceroptosis. It is commoner in women than men, and mostly after forty. The abdominal walls are usually pendulous, and as the abdominal muscles are powerful agents for keeping the abdominal viscera in place, this weakness, combined with a laxity of the hepatic ligaments, is probably the cause of the hepatoptosis. Tight lacing leads to weakness of the abdominal muscles, as well as pressing the liver down. It is flattened, often extending to the umbilicus, with its greatest prominence near the lower part and on the right. It may form a protrusion of the abdominal walls; it is easily palpable, moves up and down with respiration, and can usually be pushed back into its normal position when the patient lies down; indeed, when the patient is in the supine position it sometimes goes back of its own accord, only to fall again when she stands up.
>
> There may be no symptoms, but the patient usually complains of a dragging pain and a heaviness in the hepatic region. These are much worse in the erect posture, so that she may have always to lie down. Often, sudden attacks of pain occur in the right of the abdomen; these may be due to gall-stones or to a movable kidney, both often present with hepatoptosis, or to kinking of the bile-duct, which may lead to jaundice. As the abdominal muscles are weak, the blood stagnates in the abdominal vessels in the erect posture; hence faintness, palpitation, exhaustion, and dyspnea on exertion are common, these symptoms passing away when the patient lies down.

Received for publication Aug. 12, 1957.

CASE REPORT

Mrs. R. W., age 45 years, a farmer's wife, had been seen for complaints of vague epigastric pain off and on since September, 1956; the pain was not relieved by food or antacids. Roentgenographic studies of her stomach, small and large intestines, kidneys, and gallbladder were all normal. She received routine medications for gastritis, with poor results.

On Sept. 29, 1956, I noted that her liver was two fingers down and slightly tender. A pelvic examination was negative at this time. She continued to complain of epigastric pain and in October she was tender over the duodenum but the liver was not palpable. In November, she complained of more pain in the right upper quadrant and complained of being tired. At this time, I found her liver enlarged to three fingers below the right subcostal border. It was very tender with a sharp edge. I admitted her to the hospital on this occasion for re-evalution for possible chronic hepatitis. In the hospital, however, her liver was palpable only when she had been up and about; when she was in bed for a day, the liver was not palpable.

In the hospital, her heart rate ranged from 70 to 130. Most of the time, when I examined her, it ranged from 100 to 132. Her Decholin circulation time was 12 seconds. A fluoroscopy of the chest showed no enlargement of any chambers of the heart and no fixation of the heart. There were no murmurs. There was never at any time any sign of cardiac decompensation or angina pectoris.

After she was ambulant, her liver became palpable again and she complained more of tachycardia. She was discharged from the hospital in spite of her continuing tachycardia. Then, when I saw her in the office on November 23, her liver was very definitely enlarged to three fingers below the right costal margin and was very tender with a sharp edge.

In view of this picture of a transient, painful hepatomegaly, aggravated by the erect position, and a transient tachycardia with a sinus rhythm, this patient was investigated very thoroughly. A radioactive iodine study was normal. A therapeutic trial of digitalis produced no results. Electrocardiograms were normal. All laboratory tests, including a protein-bound iodine, calcium, phosphorus, cephaloflocculation, thymol turbidity, total cholesterol, and Bromsulphalein retention, were normal. The basal metabolic rate was normal. A urine test for carcinoid tumor was normal.

Past History.—A review of her past history revealed the same baffling train of symptoms and signs. She had an appendectomy in 1928. She had a thyroidectomy in 1935, supposedly for Graves' disease with fairly classical symptoms preceding it. A cesarean section was done in 1936, for her fourth delivery because she was told her heart "would not stand labor." And finally, in 1952, a hysterectomy was done for a prolapsed uterus.

At the time of her thyroidectomy, in 1935, she suffered from tachycardia and weakness which, although somewhat benefited by the operation, led her to return to Illinois from Colorado in 1937, one year following the cesarean section. From 1937 to 1943, she was given digitalis to be taken when needed, one pill at a time, but it was never taken over a sustained period.

Beginning in 1948, she began to suffer from attacks of severe tachycardia which would finally lead to considerable weakness and dyspnea and taper off gradually. She felt "worn out" most of the time and was hospitalized four times within a period of one year. She was given quinidine following these hospitalizations, for tachycardia, without good results.

Finally, we performed an exploratory laparotomy in January, 1957, for the transient hepatomegaly.* No abnormalities of any of the internal organs were found, except that the liver was more freely movable than normal and the surgeon could pull that organ down into the abdomen easily. A large liver biopsy was performed for the purpose of ruling out intrahepatic tumors and chronic hepatitis. The microscopic studies on the biopsy material revealed normal liver architecture.

The patient withstood the operation well and since that time has been treated with an abdominal support which tends to hold her liver up under her right thoracic cage. She has all her old symptoms, including the weakness and tachycardia, when she does not wear her abdominal support. When she does wear her abdominal support, she can work in her household with less

*Surgeon: W. F. Utterman, M.D., Perryville, Mo.

discomfort. Heavy lifting, however, still causes right upper quadrant pain and tachycardia in spite of the support. Her tachycardia is less frequent now but there is no clear-cut relationship between this symptom and the liver pain. The tachycardia occurs both at rest and on exertion and may last from moments to hours.

COMMENT

This is a report of a case of transient hepatomegaly, transient tachycardia, and right upper quadrant pain due to hepatoptosis in a normal, 45-year-old white woman.

In reviewing the details of this case, as the events have evolved during observation and therapy, it becomes apparent that her "wandering liver" has been responsible for most of her signs and symptoms for the past 20 years. Certainly, the appearance of a large, tender liver after assuming the erect position was due to hepatoptosis. The constant dragging, right upper quadrant pain, which became so annoying to the patient that she was unable to do her housework, was due to the hepatoptosis. The episodes of tachycardia, dizziness, and faintness at odd intervals for many years were due probably to the same condition. The descent of the liver, as mentioned by French, produces circulatory changes which result in tachycardia and other circulatory symptoms. Possibly, these circulatory signs are reflex in nature. It would appear possible, also, that there might be a mechanical factor involved.

This patient was studied from all possible viewpoints with the idea of discovering some occult cardiac disease, such as chronic myocarditis, thyrotoxicosis, tricuspid stenosis and insufficiency, and chronic adhesive pericarditis. All of these diagnoses and all other known cardiac diseases were satisfactorily ruled out. Also, we are convinced that none of the symptoms is psychosomatic in origin.

The logical conclusion, therefore, is that the patient's spurious cardiac condition was secondary to the circulatory changes produced by her hepatoptosis.

SUMMARY

A case of hepatoptosis resulting in right upper quadrant pain and attacks of sinus tachycardia is presented. Hepatoptosis can lead to the erroneous diagnoses of hepatomegaly, other intra-abdominal disease, and cardiac disease.

Hepatoptosis should be included in the differential diagnosis of all cases of hepatomegaly and in all other cases of epigastric and right upper quadrant distress. It should be included also in the differential diagnosis of sinus tachycardia of uncertain origin.

Hepatoptosis can be treated by the use of a proper abdominal support.

REFERENCE

1. French, H.: Index of Differential Diagnosis, Ed. 6, Bristol, England, 1945, John Wright & Sons, Ltd., p. 472.

Cyanotic Congenital Heart Disease in One of Identical Twins: Report of Two Cases

Yusuf Ziya Yuceoglu, M.D., and David T. Dresdale, M.D., New York, N.Y.

Congenital heart disease confined to one of a pair of identical twins seems to be a rare occurrence and its genesis is not well understood. It is frequently difficult to establish monozygoticity correctly and to be certain of the presence of congenital heart disease. A review of the literature, summarized in Table I, reveals that there are 20 pairs of identical twins of whom only one member of each set is affected by a congenital cardiovascular defect.[1-16]

Recently we had an opportunity to observe 2 pairs of identical twins in whom congenital heart disease affected only one member of each set. These are reported in detail because of the apparent rarity of this combination. One member of the first set of identical twins, who are girls, has "pentalogy," while the other member is completely normal. The second pair of identical twins are boys. One has "tetralogy of Fallot," while the other is normal and in good health. The congenital heart anomalies were established on the basis of clinical findings and cardiac catheterization.

CASE REPORTS

CASE 1.—E. K. was a 9-year-old white girl twin who had been born a "blue baby" after a full-term uncomplicated pregnancy. The delivery was spontaneous and her birth weight was 5.75 pounds. She was the first delivered of the twins. Her sister's weight was 5.45 pounds. At the age of 2½ months, the patient was hospitalized elsewhere because of cyanosis. Angiocardiographic study was unsatisfactory.

Unlike her twin sister she was subject to frequent attacks of upper respiratory infection characterized by fever, dyspnea, raspy cough, and coryza. The patient has been 6 months behind her sister in development, especially in standing, walking, or talking. Her exercise tolerance has always been diminished with exertional dyspnea, increase in cyanosis, squatting, and easy fatigability. She had a nonproductive cough at night. For the past 3 years she has complained of headache associated with dizziness lasting half an hour without any unconsciousness or convulsion. At the time of admission, she claimed that she became very short of breath and had to squat after walking one block or climbing one flight of stairs. She never had any ankle edema or orthopnea. There was no history of rheumatic fever or subacute bacterial endocarditis.

From the Department of Medicine, Maimonides Hospital of Brooklyn, N. Y., and the Department of Medicine, State University of New York College of Medicine, New York City.

This work was done during Dr. Yuceoglu's tenure of a Postdoctorate Fellowship of the New York Heart Association.

Received for publication Aug. 13, 1957.

TABLE I. SUMMARY OF THE REPORTS OF CONGENITAL HEART DISEASE APPEARING IN ONLY ONE MEMBER OF EACH PAIR OF IDENTICAL TWINS

AUTHOR	DIAGNOSIS OF MONOZYGOTICITY	DIAGNOSIS OF CONGENITAL CARDIOVASCULAR ABNORMALITY PROVED BY				
		CLINICAL	CARDIACI CATHETER-ZATION	ANGIO-CARDIOG-RAPHY	SURGERY	AUTOPSY
Dubreuil-Chambardel[1] (1927)	Perfect physical similarity except for the harelip showing mirror-image symmetry	Dextrocardia	—	—	—	—
Ostertag and Spaich[2] (1935)	Similarity	Congenital isolated dextrocardia	—	—	—	—
McClintock[3] (1945)	Single placenta. "There was a small placenta succenturiata. Two cords were equal in size and attached to the main placenta." The one with congenital heart disease died on the fourth day of life	PDA	—	—	—	+
Helweg-Larsen[4] (1947)	Similarity; identical blood groups; studies of fingerprints	Dextrocardia; SI of viscera	—	—	—	—
Porter[5] (1947)	Criteria was not mentioned	PDA	—	—	+	—
Jeune and Confavreux[6] (1948)	One placenta, mono-amnion, and obvious resemblance. Authors mention that it was difficult to decide about identity of infants at 2½ months of age. Moreover, the cyanotic twin died before all studies were completed	SI and maladie bleue	—	—	—	IPS; PFO; IVSD; total SI
Morison[7] (1949)	Monochorionic placenta; placental vessel anastomoses. First pair: fetuses (intrapartum stillbirth) Second pair: one is alive, normal. Other fetus (intrapartum stillbirth)	— —	— —	— —	— —	POAC; DA; HLV; SCAIT; and other extracardiac abnormalities and CB with imperfect incorporation of SV and BC; DEFT

Lamy and Schweisguth[8] (1950)	Criteria was not mentioned	First pair: Roger's disease Second pair: PDA	Not mentioned			
Forsyth and Uchida[9] (1951)	Similarity; identical blood groups; dermal configurations (analysis of digital, palmar, plantar configurations)	IASD	+	—	—	—
Goldman and Stern[10] (1952)	Similarity; monochorionic pregnancy	IASD	—	—	—	—
Wade[11] (1952)	Similarity; identical blood groups; studies of fingerprints	First pair: PDA Second pair: IPS	— —	— —	+ —	— —
Starer[12] (1953)	Not mentioned	PDA	—	—	+	
Anderson[13] (1954)	Anthropomorphic data; identical blood groups	First pair: PDA Second pair: PDA	— —	— —	+ +	— —
Stadler[14] (1955)	Similarity; one placenta	Dextrocardia of mixed type	—	—	—	—
Stadler and Chroniak[15] (1956)	Similarity; identical blood groups	IASD and tetralogy of Fallot	—	—	—	—
Paes[16] (1956)	Similarity; one placenta	Pseudotruncus arteriosus	—	+	—	—

PDA: Patent ductus arteriosus
IVSD: Interventricular septal defect
IPS: Infundibular pulmonic stenosis
PFO: Patent foramen ovale
SI: Situs inversus
POAC: Persistent ostium atrioventriculare communis
DA: Dextroposition of the aorta
HLV: Hypoplasia of the left ventricle
SCAIT: slight coarctation of the aorta of infantile type
CB: Cor biloculare
SV: Sinus venosus
BC: Bulbus cordis
DEFT: Diffuse endocardial fibroelastic thickening
IASD: Interatrial septal defect

The mother was 36 years old at the time of delivery of the patient. She had had a spontaneous abortion at 3 months, and an incomplete abortion at 3 months before becoming pregnant with the twins. Her period of gestation with the twins was uneventful. There is no family history of congenital heart disease.

Physical examination of the patient on admission revealed a thin, underdeveloped and intensely cyanotic white girl who was not in acute distress (Fig. 1). Her weight was 45 pounds,

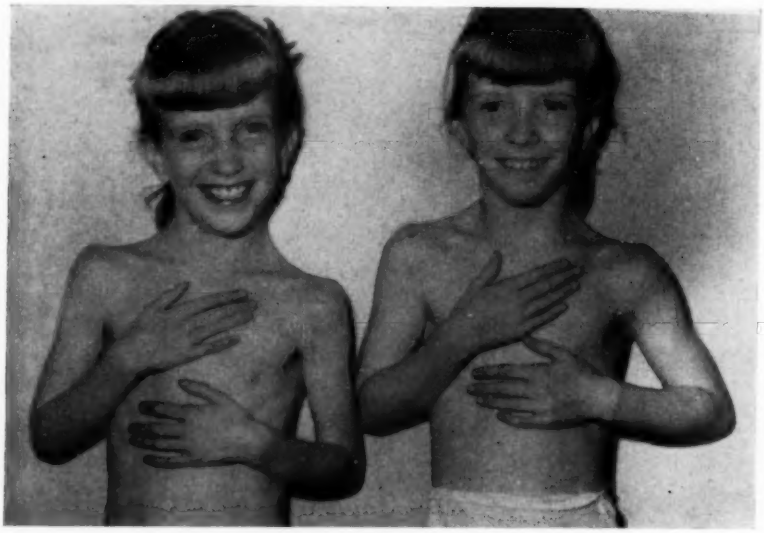


Fig. 1.—Case 1. Twin sisters. The patient is on the left.

and her height was 51 inches. Her pulse was 90 per minute and regular. The temperature was normal. The blood pressure in right and left upper extremities was 80/60 and 90/60 mm. Hg, respectively. The blood pressure in the right leg was 110/84 mm. Hg and in the left leg 108/78 mm. Hg. Tonsils were enlarged. There was no venous distention. The chest was thin and the lungs were clear. A diffuse apical impulse was in the fourth to fifth intercostal space inside the left mid-clavicular line. The second sound in the pulmonic area was accentuated and louder than the aortic second sound. There was a Grade 3 rough systolic murmur over the precordium, loudest in the third and second left parasternal spaces. There was no radiation in the neck or back. There was no thrill. Liver, spleen, and kidneys were not palpable. Cyanosis and clubbing of the fingers and toes were present.

Hemoglobin content of the blood was 18.9 Gm. per 100 c.c. Red blood cells numbered 6 million with a hematocrit of 67 per cent. Erythrocyte sedimentation rate was 1 mm. in one hour. Blood chemistries and urine were all normal.

Electrocardiogram showed evidence of right ventricular hypertrophy (Fig. 2).

Fluoroscopic examination and roentgenologic studies of the chest showed right ventricular enlargement and concavity in the region of the pulmonary artery. The right hilar shadow was poorly formed and the parahilar vascular markings were irregular and of wiry appearance. The left hilar shadow was somewhat longer but was also irregularly formed and the parahilar vascular markings were diminished in prominence. Peripheral pulmonary vascular markings were diminished (Fig. 3). Angiocardiography revealed simultaneous visualization of the aorta and pulmonary artery when the radiopaque substance was injected into the right ventricle.

Cardiac catheterization was done with the patient under Pentothal anesthesia. The catheter passed from the right atrium to the left atrium and left ventricle with ease. The mean pressure was 4 mm. Hg in the left auricle and 3 mm. Hg in the right during continuous tracing. Right ventricular pressure was markedly elevated to 85/6 mm. Hg. The simultaneous pressures in

the right ventricle and right brachial artery were 85/6 and 83 mm. Hg systolic, respectively. Pulmonary "capillary" pressure was 5 mm. Hg. The pulmonary artery mean pressure was low, 10 mm. Hg. Pressure measurements made in the left ventricle and right brachial artery simultaneously were 80/6 and 81/58 mm. Hg, respectively. There was a high pressure gradient as the catheter was withdrawn from the pulmonary artery into the right ventricle, and the tracing showed a sudden and only a single change in pressure. Brachial artery pressure pulse did not show any abnormality in contour.

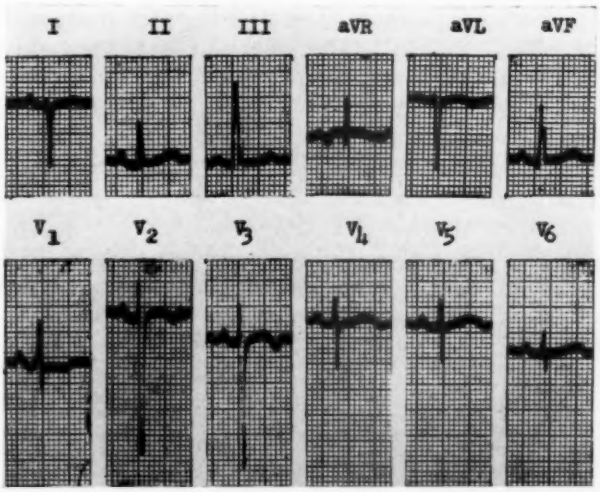


Fig. 2.—Case 1. E.K., 9-year-old girl. Electrocardiogram taken on Oct. 3, 1955.

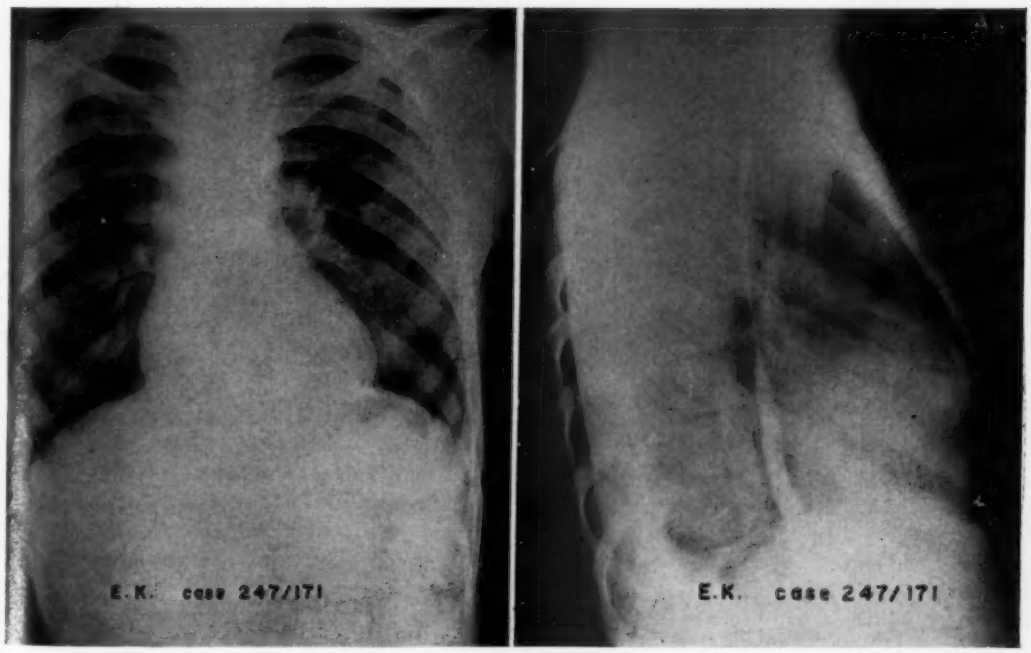


Fig. 3.—Case 1.

Blood samples obtained in rapid sequence from inferior vena cava, superior vena cava, and right auricle showed an oxygenation of the blood in the right auricle. The oxygen content of the blood taken from the right auricle was 1.4 vol. per cent higher than the average of the inferior vena cava and superior vena cava bloods. The oxygen content of the bloods taken from left auricle was 88 and 83 per cent saturated at two different times. Blood samples taken from the left ventricle and brachial artery simultaneously were 79 per cent saturated. There was an increase of 0.5 vol. per cent in the oxygen content of the blood taken from the right ventricle as compared with that from the right auricle. Brachial artery oxygen saturation at rest was low, 73 and 77 per cent, with further decrease to 55 per cent when the patient was restless.

Cardiac catheterization was performed again with the patient under Pentothal and ether anesthesia on Oct. 27, 1955, for the purpose of injecting radiopaque solution, Urokon* into the right ventricle in order to determine radiologically whether or not overriding of the aorta was present. At this time the pulmonary venous blood was 95 per cent saturated when femoral artery blood saturation was 66 per cent.

Pressure studies revealed the following: pulmonary vein "wedge" pressure 4.5 mm. Hg, left auricle 4 mm. Hg, and right auricle 3 mm. Hg. These findings, as in the first study, indicate a left-to-right pressure gradient at the level of the auricles.

The hemodynamic data are consistent with pulmonic stenosis of the valvular type, intracardiac left-to-right and right-to-left shunts through an interatrial septal defect, and right-to-left shunt due to a high interventricular septal defect and overriding of the aorta. The above data is compatible with the diagnosis of tetralogy associated with interatrial septal defect (pentalogy).

The twin sister (J.K.) was a normal, thin, healthy girl who was slightly taller and heavier than the patient just described. Her height was 52¼ inches and her weight was 51 pounds. She was 1 inch taller and weighed 6 pounds more. There were no abnormal physical findings. Electrocardiogram and chest x-ray were normal. She closely resembled her twin sister with congenital heart disease. Color, texture and form of their hair, eye color, pigment pattern of iris, features of the nose, lips, chin, ears, types of teeth, body proportions, etc., were similar. Skin color was also the same, except that the one with congenital heart disease was cyanotic (Fig. 1).

Blood grouping, subgrouping, MNS, Rh, Kell, Duffy, P typings showed no difference between their blood. Their mother's blood revealed difference on P typing (Table II). Their father's blood could not be obtained.

Their fingerprints were reported not to be similar.[17]

TABLE II. THE BLOOD TYPING OF MRS. K. AND THE TWINS

	GROUP	D	C	E	c	M	N	P	K	F_{ya}
Mrs. K.	A_1	+	+	+	+	+	0	+	0	0
J.K.	A_1	+	+	+	+	+	0	0	0	0
E.K.	A_1	+	+	+	+	+	0	0	0	0

CASE 2.—A. M. is a 9-year-old white boy who has had a murmur since birth. He was the second of the twins delivered by cesarean section at the end of 7 months of gestation. His birth weight was 2,272 grams and his height 43 cm., whereas his twin brother's height was 42 cm. and weight 1,830 grams. Cyanosis was not noted at birth. He has had rather frequent sore throats and upper respiratory infections. As a child he did not eat well. His growth has been poor as compared with his twin brother's. Cyanosis was first noticed by his mother when he started to

*Registered trademark.

walk. It was noted that as he grew older and became more active the cyanosis became more noticeable. However, there was no limitation in his activity until he entered elementary school where it was noticed that the child became cyanotic and had to stop to squat at play. Thereafter, he was placed in a special class and given limited physical activity. About 9 months prior to admission to the hospital he suddenly developed convulsions associated with unconsciousness and, a few days later, severe headache and fever. He was hospitalized in another hospital where he was treated medically for "brain abscess," with complete recovery. At the time of admission, the child was unable to climb a flight of stairs.

He stood at 9 months, walked at 1 year of age, talked in phrases at 2 years of age. His past illnesses consisted of measles, German measles, chicken pox, and mumps. The mother's age was 32 at the time of delivery. She had a stillbirth 3 years prior to the patient's birth. There was no history of any disease during pregnancy. There was no family history of congenital heart disease. The patient's sister, as well as the twin brother, are in good health.

Physical examination revealed a thin, somewhat underdeveloped, though mentally alert boy with mild cyanosis of the lips, tongue, fingers, and toenails. There was questionable clubbing. Temperature was 96.4°F., pulse rate 90, respiration 20 per minute. Blood pressures were 108/80 mm. Hg in both arms and 126/90 mm. Hg in both legs. His weight was 54 pounds and his height 51 inches—17 pounds lighter and 1.5 inches shorter than his twin brother. The tonsils were enlarged without evidence of inflammation and uvula bifid. The neck veins were not distended.

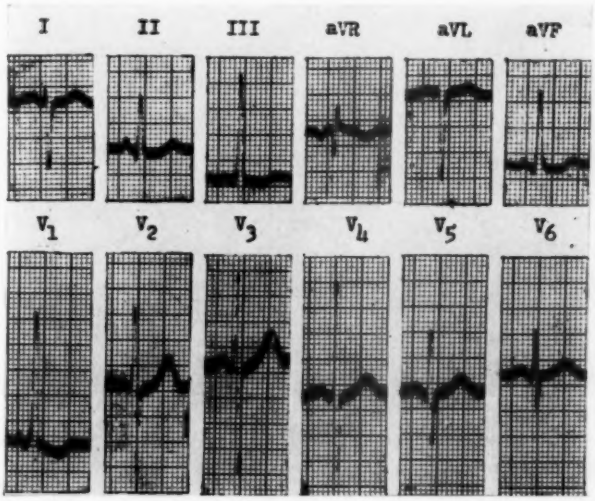


Fig. 4.—Case 2. Electrocardiogram of A.M., on Jan. 26, 1956.

The lungs were clear. There was a barely palpable apical impulse in the fourth intercostal space inside the mid-clavicular line. A slight systolic thrill was felt in the second intercostal space, to the left of the sternum. The first sound was normal. The pulmonic second sound was split, with its second component being diminished in intensity and less than the aortic second sound. There was a harsh, loud Grade 4 systolic murmur all over the precordium, maximal in the second intercostal space to the left of the sternum. This murmur was transmitted upward to the neck vessels and left suprascapular area.

The liver, spleen, and kidneys were not palpable. The peripheral pulses were strong and there was no edema.

Laboratory data included: hemoglobin 14.4 Gm.; erythrocyte count 4.8 million; hematocrit 43 per cent; and leukocyte count 7,100 with a normal differential.

The electrocardiogram showed the characteristic pattern of right ventricular hypertrophy (Fig. 4).

The roentgenogram and fluoroscopic examination of the chest showed the heart to be not significantly enlarged on the posteroanterior view. The apex was elevated and the pulmonary artery segment was prominent. There was a distinct and prominent concavity along the upper left border of the heart. Left hilar vessels were prominent with good systolic expansion on fluoroscopy. Right hilar vessels were within normal limits. Perihilar vessels and peripheral vasculature of lungs were diminished. The aorta was prominent and hyperpulsating. The oblique and lateral views revealed enlargement of the right ventricle and prominent main pulmonary artery. There was no evidence of left ventricular enlargement (Fig. 5).

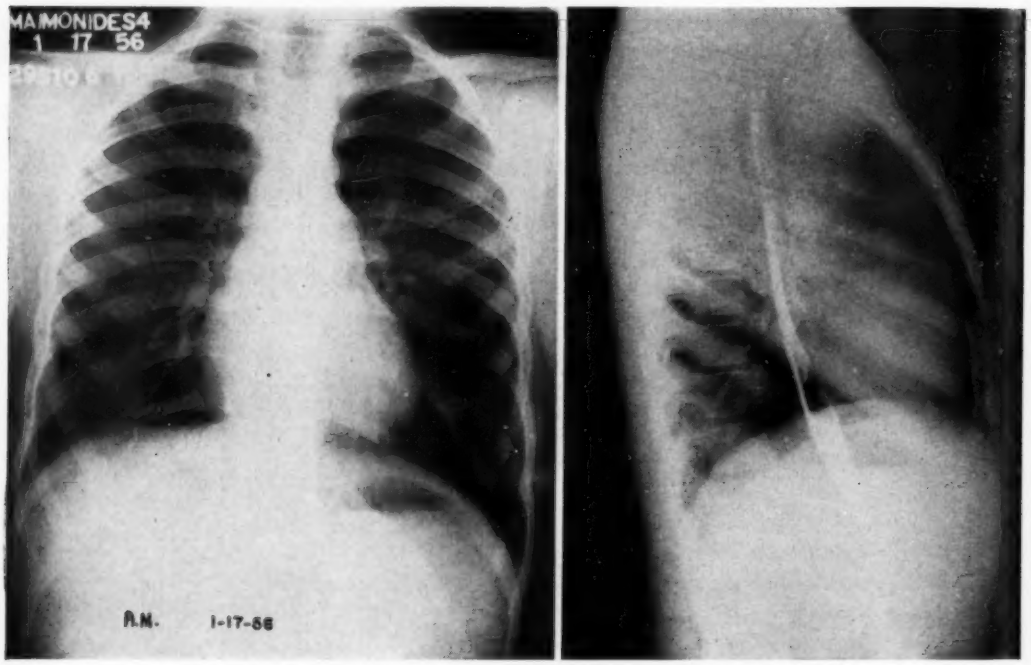


Fig. 5.—Case 2.

Cardiac catheterization was performed on Jan. 26, 1956, with the patient under Pentothal anesthesia. A No. 7 catheter was introduced through a left median basilic vein cut-down. Since it was impossible to enter into the superior vena cava this way, a right median basilic vein cut-down was done. The right heart chambers and the aorta were entered but the catheter could not be introduced into the pulmonary artery.

Systolic right ventricular pressure was markedly elevated, 92 mm. Hg on different occasions, while the end-diastolic pressure in the right ventricle was 8 and 5 mm. Hg. On another occasion, while the catheter was withdrawn from right ventricle to right auricle, ventricular end-diastolic pressure was 4 mm. Hg and equal to mean right auricular pressure. Right ventricular systolic pressure was 92 mm. Hg and aortic systolic pressure was 93 mm. Hg as the catheter was withdrawn from the aorta into the right ventricle. Simultaneous aortic and right femoral artery pressures were 96/78 and 96/70 mm. Hg, respectively. Right femoral artery and aortic pressure pulses did not show any abnormality in their contour.

Blood samples obtained in rapid sequence from the aorta, right ventricle outflow tract, right ventricular apex, and right auricle showed an oxygenation of the blood in the right ventricle. The oxygen content of the blood taken from the right ventricular outflow tract was 2.8 vol. per cent higher than the blood obtained in the right ventricular apex, 2 vol. per cent higher than that obtained from the right auricle, and 0.9 vol. per cent less than the blood obtained in the aorta. There was no change in O_2 content between right auricle and both venae cavae.

Femoral artery and aortic blood oxygen saturations at rest were low, both 89 per cent, with further decrease to 81 per cent toward the end of the procedure.

The foregoing data in conjunction with the x-ray and clinical findings are consistent with the diagnosis of tetralogy of Fallot.

P.M., the twin brother of the patient, was a normal, healthy boy. His height was 52.5 inches and his weight was 71 pounds. Physical examination revealed no abnormality. Electrocardiogram and chest x-ray (cardiac series) were normal. He was strikingly similar in general appearance to his mate with congenital heart disease, except for slight difference in height and obvious difference in weight. Hair color, texture and form, face, nose, lips, chin, ears, type of teeth, pigment pattern of iris, type and proportions of hands, fingers and toes, etc., were alike (Fig. 6). Skin color was also the same except the one with congenital heart disease showed cyanosis on exertion.

Fig. 6.—Case 2. Twin brothers. The boy on the left is the one with congenital heart disease. This picture was taken fifteen months after the study since an earlier photograph was lost.

Careful studies of their bloods concerning blood grouping, subgrouping, MNS, Rh, Kell, Duffy and P typings showed no difference whatsoever, whereas their parents' bloods were serologically different (Table III). Their fingerprints were also reported not to be identical.[17]

TABLE III. THE BLOOD TYPING OF MR. M., MRS. M., AND THE TWINS

	GROUP	D	C	E	c	e	M	N	P	K	F^{ya}
Mr. M.	A_1	+	+	0	+	+	+	+	+	0	+
Mrs. M.	B	+	0	+	+	+	+	+	0	0	+
P.M.	A_1B	+	+	0	+	+	0	+	+	0	0
A.M.	A_1B	+	+	0	+	+	0	+	+	0	0

DISCUSSION

The diagnosis of identity is of paramount importance since superficial resemblance may lead to an erroneous conclusion. The diagnosis of identity in our cases was based upon the "similarity method," which was described in detail by Newman,[18,19] and by identity of blood groups. The twins were strikingly similar in every way to each other, making it impossible to distinguish one from the other except by those features contributed to by the heart disease, such as cyanosis and the differences in height and weight. The affected twins are somewhat shorter and weigh less than their normal mates. It is interesting to note that the birth weights of both affected twins were more than those of the normal twins. We do not know E. K.'s height at birth, but A. M. (the affected twin) was 1 cm. taller than his normal twin brother. This would suggest that in utero the physical development of the affected twins was not adversely affected. However, postnatal development of the affected twins has not been as good as their mates. Underdevelopment is not an unusual condition in patients with congenital heart disease, especially with a right-to-left shunt causing systemic anoxemia. In some patients with congenital heart disease marked growth retardation postnatally was attributed primarily to genetic or in utero factors.[20]

It has been stated that the diagnosis of identical twins by means of "similarity method" can be made in 97 to 98 per cent,[21] or 99 per cent[22] of the cases. There remains 1 to 2 per cent of the cases in which the diagnosis is in doubt. Where more information is necessary, Newman[21] suggested using palmar dermatoglyphics and fingerprints as an additional aid, but not as a criterion for the diagnosis. He later made the statement, "The general character of pattern and main lines of finger and palm prints must be essentially the same," and considered this similarity as a criterion.[19] Komai and Fukuoko[23] found in a set of dichorionic identical triplets that their finger patterns closely matched yet were different from those of their parents and other siblings. On the other hand, Cummins and Mairs[24] noted marked differences in the fingerprints of conjoined twins. In Wade's cases,[11] fingerprints were not identical, but "marked similarity" was found. The palm and fingerprints of our cases were studied by the Federal Bureau of Investigation and were reported to be not identical.[17] According to the Federal Bureau of Investigation[25] identical fingerprints have never been found in monozygotic twins. This point has been emphasized also by Cummins and Midlo.[26] The F.B.I.[25] points out that while twins may have the same type of fingerprint pattern in corresponding fingers, different persons may also have such similarities. However, the ridge details of the fingerprints, the only absolute proof of identity, are not identical. For this reason palm and fingerprints cannot be used for the diagnosis of identity.

Blood groups have also been used in distinguishing monozygotic from dizygotic twins. It is well known that identical twins must have identical blood groups. Therefore, if the blood groups are different, the twins are not identical and the problem is easily solved; but the reverse is not necessarily true. For this reason in such cases, blood groups, subgroups, and other factors as well as parents' and other siblings' blood should be identified. Chances for possible identity can be calculated, especially if the blood groups of the parents are

known.[27,28] The blood groups of the twins reported here are identical but they differ from those of their parents (Tables II and III). The survival of skin homografts[29,30] between identical twins can furnish additional evidence for their immunologic and genetic identity.

The characteristics of the placenta, chorion, and amnion can also be used for the diagnosis of monozygoticity. The presence of one placenta and one chorion, one amnion, or one chorion and two amnions is almost conclusive evidence of identity.[22,31] Information concerning afterbirths was not available in the charts of the cases reported here.[32]

Platt and Lawton[33] studied the retinae of identical and nonidentical twins by fundus photography, hoping to discover differences permitting the distinction between monozygotic and dizygotic twins. A general similarity in the fundus structure was usually found in the monozygotic pairs. But they concluded that this could not be used as a specific test of zygoticity.

Twins are either identical or nonidentical. Nonidentical twins (also called polyovular or dizygotic) arise from two ova fertilized by two sperms. Thus, the resultant genetic constitution of the fertilized ova bear no more resemblance to each other than would be expected of any other two siblings in the same family. It would not be unusual to observe a congenital abnormality in only one of them. On the other hand, identical, monovular, (uniovular or monozygotic) twins result from separation of a single zygote and have the same genotype. Since intrauterine environment, in a general way, is also the same for both twins, they have the same phenotype and are alike in every way. Therefore, a congenital cardiac abnormality involving one of identical twins theoretically should be present also in the other. This has been observed.[12,34-38] As seen from the two cases reported here and those cited in the literature, congenital heart disease may, in fact, affect only one of monovular twins. It is not very easy to explain the genesis of this discordance. Although advances have been achieved in the diagnosis, understanding of the hemodynamics, and treatment of congenital heart disease in the past decade, little is known about the genesis of the congenital malformations of the heart.

The causes of congenital defects in general and "developmental mechanics of heart malformations" have recently been the subject of extensive reviews by Ingalls,[39] Mautner,[40] and others.[41-43] The causes are genetic and/or environmental. The importance of genetic factors in the occurrence of congenital heart disease has long been known. There are many reports in the literature regarding the familial incidence of congenital heart disease.[8,44-53] Congenital heart disease among brothers and sisters has been mentioned.[44] Taussig[45] observed 4 families with congenital heart disease. In 2 of these families the disease was transmitted to more than one generation. A father and 4 of his 8 children with signs of patent ductus arteriosus, and a mother and fetus with identical high interventricular septal defect were described by Walker and Ellis.[46] Stein and Barber[47] reported the case of a mother with coarctation of the aorta, whose son and daughter had signs of patent ductus arteriosus. Campbell[48] observed a mother with patent ductus arteriosus, whose daughter had coarctation; he also mentioned a family with signs of interatrial septal defect in 3 generations. Lamy and Sch-

weisguth[8] recorded the case of a mother with ventricular septal defect and patent ductus arteriosus, whose daughter also had patent ductus arteriosus. Joyce and O'Toole[49] reported on 4 siblings each with congenital heart disease. Three of them had patent ductus arteriosus and one cyanotic heart disease. A father and his son with coarctation of the aorta has been reported by Walker.[50] "Patent ductus arteriosus" in 2 sisters was presented by Ellis.[51]

The description in the literature of families with congenital heart disease may suggest the presence of a genetic background. While it may not be reasonable to draw a definite conclusion in this regard in view of the fact that these reports concern isolated families, large-scale studies of families with congenital heart disease would tend to support this concept. Lamy and Schweisguth[8] reported a familial incidence of cardiac malformations in 8 per cent of 304 patients with congenital heart disease. McKeown and his associates[54] found an increase in the incidence of congenital heart disease among siblings born after first propositi. This was about 6 times the incidence of the general population at birth. A tendency for familial occurrence has also been shown by Anderson[13] in a large series of patients with patent ductus arteriosus. Polani and Campbell,[55] in a statistical study of 377 families having children with congenital heart disease, found that the incidence of congenital cardiac malformations among brothers and sisters born after the index cases increased to about 20 times the incidence in the general population. All of the aforementioned observations and studies suggest that the incidence of congenital heart disease among descendants of a family with congenital heart disease is more common than would be expected by chance.

Rösler,[56] in 1928, in a series of 60 cases of congenital heart disease, found consanguinity present in 10 per cent. However, this high incidence of consanguinity was not confirmed by Campbell.[48] He found consanguineous marriages in only 1.5 per cent of his 250 patients with cyanotic congenital heart disease as compared to 0.6 to 0.9 per cent in the general hospital population. He thought this difference in incidence was not definitely significant. Cockayne[57] found that dextrocardia with transposition of the viscera was more common after first-cousin marriages and he thought that this was an inherited recessive character. Later, this view was supported by McKeown and his associates.[54] The incidence of consanguinity among the parents of congenital cardiacs was estimated to be 3.3 per cent by Lamy and Schweisguth.[8] Polani and Campbell[55] found that the incidence of first-cousin marriages among the parents of patients with congenital heart disease was 0.8 per cent as against 0.4 per cent of a hospital population. They felt this was not a significant difference, but did consider it "identical with the percentage to be expected on the hypothesis that congenital heart disease resulted from simple autosomal recessive inheritance."

Environmental factors have also been shown to play a role in the causation of congenital heart disease. Maternal rubella is an important factor in some cases. In a study of 78 cases of congenital cataract occurring after maternal rubella during the first 2 months of pregnancy, Gregg[58] noted that congenital heart abnormalities were present also in 44. There were 17 cardiac anomalies in 31 cases of congenital defects following maternal rubella in the series reported

by Swan and his associates.[59] Swan[60] reviewed the literature in 1949. He concluded that "a woman who contracts rubella during the first four months of pregnancy has a three to one chance of giving birth subsequently to a congenitally defective infant." Recently, others[61,62] have also shown the importance of maternal rubella in the etiology of congenital heart disease. On the other hand, Campbell[48] found only 4 instances of congenital heart disease (all cyanotic) following maternal rubella among 250 cyanotic and 50 acyanotic congenital heart disease cases.

Exposure of the pregnant mother to x-ray[63] or radium irradiation[64] has been cited as a causative factor for other types of congenital abnormalities. The atomic bomb[65,66] had been incriminated in some congenital abnormalities such as microcephaly with mental retardation. However, Sutow and West[67] in a comparative study of skeletal abnormalities could not find any difference in incidence between children who had been exposed to the atomic bomb while in utero and those who had not been exposed. Recently, Macht and Lawrence[68] made a statistical study based on questionnaires sent to radiologists and other physicians comparing their offspring. Their subjects were chiefly males. They found a significantly higher percentage of congenital defects, including congenital cardiovascular abnormalities, in the offspring of the group exposed to x-rays than in the offspring of unexposed controls.

In one case, cortisone therapy in early pregnancy was suspected in the occurrence of a cleft palate in the offspring.[69] Some abnormalities such as hydrocephalus, meningoencephalocele, and cleft palate with harelip have been observed by Thiersch[70] in human embryos following therapeutic abortions with a folic acid antagonist. In some instances toxoplasmosis[71] of the mother, poisoning, trauma, etc.,[39] and age of the mother,[39,55] (which is associated in the older group with more bleeding, genital disease) have been accused. Recently, Davis and Potter[72] found that the incidence of congenitally malformed babies is not only more common in mothers above 35 years of age, but that it is also more common in mothers below 20 years of age than in middle-aged mothers. Increased father's age may be of significance also, as is seen in achondroplasia.[73] The seminal fluid of fathers of children with congenital abnormality studied by Takala[74] showed a higher incidence of abnormal forms of sperm, which might be of importance. Mutation seems to be another factor in the causation of congenital abnormalities.[73,75-78]

Many congenital abnormalities can be produced experimentally in animals. Stockard,[79] in 1921, in his excellent experimental study on the eggs of fish, found that developmental arrest induced by temporarily lowering the temperature of the surroundings or by a low oxygen concentration during the critical stage of development resulted in congenital abnormalities. Warkany,[80] in 1944, showed in female rats that maternal nutritional deficiency (vitamin A, riboflavin) may lead to congenital malformations such as blind or deformed eyes, skeletal changes, and cleft palate. Cardiovascular abnormalities, in addition to others, have been induced in the offspring of rats fed vitamin A deficient diets during pregnancy.[81,82] Riboflavin,[83-85] pteroylglutamic acid,[86-88] pantothenic acid,[89-91] vitamin E deficiency[92] in pregnant rats also may cause various abnormalities, including cardiovascular ones, in the offspring. A high incidence of hydrocephalus,

spina bifida, cleft palate, etc., was produced in rats experimentally injected with trypan blue solution before conception and during pregnancy.[93] Wilson,[94] in addition to those defects, was able to produce cardiovascular abnormalities in the offspring of rats with the injection of azo-dyes. Some congenital abnormalities, especially cleft palate, can be induced in the offspring of pregnant mice by the administration of cortisone.[95-97] The authors have found also that the frequency of the abnormality depends upon the genotype of the animal ("some strain is susceptible"), the dose of the cortisone, and the time of the treatment during gestational period. Irradiation of the developing embryo by exposing the pregnant animal to x-ray has also been shown to produce some malformations such as anencephaly, craniocerebral defects, cleft palate, and skeletal deformities, etc.,[98-102] and even cardiac anomalies.[103] In almost all experimentally produced congenital abnormalities there is a stage of development of the embryo, called the "critical stage," when the development can be influenced or interrupted by an environmental factor. The environmental factor is effective particularly in this stage. In man, this stage for most congenital malformations is probably in the first 6 to 8 weeks of gestation.

All the foregoing data indicate that genetic and/or environmental factors are effective in the production of congenital malformations. How closely these factors tie in with each other to produce congenital abnormalities is not clearly known in all cases. While genetic factors are important in the production of congenital abnormalities, in many cases environmental factors are of paramount importance, either by making manifest an abnormal pre-existent genetic abnormality or independently causing an abnormality by direct noxious effect on the developing embryo.

The two cases reported in this paper do not have any familial incidence of congenital heart disease to suggest a genetic background. The relatively older age of the mothers, history of spontaneous abortions of one mother, and history of stillbirth of the other mother may be significant. But a definite conclusion cannot be made from these. The negative genetic and uncertain environmental history in the cases reported here does not definitely rule out one or both of these factors as possible causes. However, observation of a congenital heart disease in only one of identical twins is difficult to explain. How can congenital cardiac defect affect only one of the identical twins when both have the same genes? The answer is speculative. Since the genes are the same in both, some other factor, probably environmental, should be present making manifest a latent genetic abnormality of both of the twins by influencing this factor in only one of them. On the other hand, theoretically, they have the same environment in the uterus. Perhaps in reality, this is not so. One of the undetected environmental factors may perhaps affect only one of the twins for some unknown reason. It is also quite possible that without any genetic abnormality, an environmental factor by itself may cause the congenital malformation in one of them by producing a developmental abnormality for a short period of time in early intrauterine life. This factor may be, for instance, a nutritional deficiency caused by bleeding of the placenta or an abnormally inserted cord at the site of the affected fetus. Brody[104] found marked differences in size and weight of 4 cases of monochorial

twins. It is interesting that the smaller twin of each set had abnormally inserted cords. In contrast, in our cases the affected twins' birth weights were more than their normal mates. However, no information is available about the fetal membranes of our cases.

Further observations and detailed study of such cases are needed for better understanding of the genesis of this complex problem.

SUMMARY

1. Two pairs of identical twins are reported. One twin of each pair had cyanotic congenital heart disease. The other twin was completely normal. One set of twins was girls and the other, boys. The affected twin had pentalogy in the first pair, tetralogy of Fallot in the second pair. They were 9 years of age at the time of the examination. The diagnosis of congenital heart disease was established by clinical findings and cardiac catheterization.

2. No detectable genetic history or definite environmental factors could be established in either pair.

3. The monozygoticity of the twins was based on the "similarity method" as well as serologic identity.

4. The finger- and palmprints of these twins were not identical. Uselessness of the finger- and palmprints as a diagnostic test in distinguishing identical from nonidentical twins has been emphasized.

5. The literature concerning congenital heart disease affecting only one of identical twins and the causes of congenital heart diseases have been reviewed. No definite explanation could be concluded for the congenital heart disease involving only one of the identical twins.

The authors wish to express their appreciation to Dr. Max Michael, Jr., for reviewing this paper and for his valuable suggestions.

REFERENCES

1. Dubreuil-Chambardel, L.: Presse méd. **35**:877, 1927.
2. Ostertag, M., and Spaich, D.: Ztschr. f. menschl. Vererb.-u. Konstitutionslehre **19**:577, 1935.
3. McClintock, K.: Arch. Dis. Childhood **20**:47, 1945.
4. Helweg-Larsen, H. F.: Ann. Eugenics **14**:1, 1947.
5. Porter, W. B.: Am. J. M. Sc. **213**:178, 1947.
6. Jeune, M., and Confavreux, J.: Arch. franç. pédiat. **5**:252, 1948.
7. Morison, J. E.: Arch. Dis. Childhood **24**:214, 1949.
8. Lamy, M., and Schweisguth, O.: Ann. paediat. **174**:65, 1950.
9. Forsyth, C. C., and Uchida, I.: Arch. Dis. Childhood **26**:582, 1951.
10. Goldman, I. R., and Stern, N. S.: Am. Heart J. **44**:159, 1952.
11. Wade, G.: Brit. Heart J. **14**:475, 1952.
12. Starer, F.: Brit. M. J. **1**:971, 1953.
13. Anderson, R. C.: Pediatrics **14**:143, 1954.
14. Stadler, H. E.: J. Pediat. **47**:353, 1955.
15. Stadler, H. E., and Chroniak, W.: J. Pediat. **49**:450, 1956.
16. Paes, O. de O.: Am. Heart J. **52**:929, 1956.
17. Hoover, J. E. (Director, F.B.I.): Report on fingerprints of cases studied.
18. Newman, H. H.: Biol. Bull. **55**:283, 1928.
19. Newman, H. H.: Multiple Human Births; Twins, Triplets, Quadruplets and Quintuplets, New York, 1940, Doubleday, Doran & Co., Inc.
20. Adams, F. H., Lund, G. W., and Disenhouse, R. B.: J. Pediat. **44**:674, 1954.
21. Newman, H. H.: J. Hered. **22**:41, 1931.

22. Stern, C.: Principles of Human Genetics, San Francisco, 1950, W. H. Freeman and Company, chapter 23.
23. Komai, T., and Fukuoko, G.: J. Hered. **22**:233, 1931.
24. Cummins, H., and Mairs, G. T.: J. Hered. **25**:237, 1934.
25. F.B.I. Law Enforcement Bulletin, February, 1953: "Those Fingerprints of Identical Twins Are Not Identical!"
26. Cummins, H., and Midlo, C.: Fingerprints, Palms and Soles, An Introduction to Dermatoglyphics, Philadelphia, 1943, Blakiston Company.
27. Race, R. R., and Sanger, R.: Blood Groups in Man, Ed. 2, Oxford, 1954, Blackwell Scientific Publications.
28. Smith, S. M., and Penrose, L. S.: Ann. Human Genet. **19**:273, 1955.
29. Brown, J. B.: Surgery **1**:558, 1937.
30. Merill, J. P., Murray, J. E., Harrison, J. H., and Guild, W. R.: J.A.M.A. **160**:277, 1956.
31. Potter, E. L.: Pathology of the Fetus and Newborn, Chicago, 1952, The Yearbook Publishers, Inc.
32. Fekete, L. A.: Personal communication.
33. Platt, R., and Lawton, R.: Ann. Human Genet. **21**:132, 1956.
34. Smith, K. S.: Arch. Dis. Childhood **4**:330, 1929.
35. Giustra, F. X., and Tosti, V. G.: Am. Heart J. **17**:249, 1939.
36. Kean, B. H.: J. Hered. **33**:217, 1942.
37. Campbell, M.: Guy's Hosp. Gaz. **58**:228, 1944.
38. Benesova, D., and Sikl, H.: J. Path. & Bact. **67**:367, 1954.
39. Ingalls, T. H.: J.A.M.A. **161**:1047, 1956.
40. Mautner, H.: Arch. Pediat. **73**:47, 1956.
41. Warkany, J., Guest editor, and others: Supplement to Pediatrics **19**:719-792, 1957.
42. Reynolds, S. R. M., Wolff, H., Dancis, J., and Smith, C. A.: Mechanisms of Congenital Malformation, Proceedings of the Second Scientific Conference of the Association for the Aid of Crippled Children, June 15 and 16, 1954, New York, 1955, John B. Watkins Company.
43. Holt, L. E., Ingalls, T. H., Hellman, L. B.: Prematurity, Congenital Malformation and Birth Injury, Proceedings of a conference sponsored by the Association for the Aid of Crippled Children at the New York Academy of Medicine, June 5 and 6, 1952, New York, 1953, John B. Watkins Company.
44. Osler's Modern Medicine, Ed. 3, Vol. 4: Abbott, M. E.: Congenital Cardiac Disease, Philadelphia, 1927, Lea & Febiger.
45. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.
46. Walker, G. C., and Ellis, L. B.: Proceedings of the New England Heart Association, 1940-1941, p. 26.
47. Stein, I., and Barber, D. J.: Am. Heart J. **30**:118, 1945.
48. Campbell, M.: Quart. J. Med. **18**:379, 1949.
49. Joyce, J. C., and O'Toole, S. P.: Brit. M. J. **1**:1241, 1954.
50. Walker, W. G.: New England J. Med. **211**:1192, 1934.
51. Ellis, R. W. B.: Brit. J. Child. Dis. **33**:286, 1936.
52. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, The Yearbook Publishers, Inc.
53. Brown, J. W.: Congenital Heart Disease, Ed. 2, New York, 1950, Staples Press.
54. McKeown, T., MacMahon, B., and Parsons, C. G.: Brit. Heart J. **15**:273, 1953.
55. Polani, P. E., and Campbell, M.: Ann. Human Genet. **19**:209, 1955.
56. Rösler, H.: Wien. Arch. f. inn. Med. **15**:495, 1928.
57. Cockayne, E. A.: Quart. J. Med. **7**:479, 1938.
58. Gregg, N. McA.: Tr. Ophth. Soc. Australia **3**:35, 1941.
59. Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B.: M. J. Australia **2**:201, 1943.
60. Swan, C.: J. Obst. & Gynaec. Brit. Emp. **56**:341, 1949; **56**:591, 1949.
61. Gibson, S., and Lewis, K. C.: A.M.A. Am. J. Dis. Child. **83**:317, 1952.
62. Stuckey, D.: Brit. Heart J. **28**:519, 1956.
63. Murphy, D. P.: Congenital Malformations, A Study of Parental Characteristics With Special Reference to the Reproductive Process, Ed. 2, Philadelphia, 1947, J. B. Lippincott Company.
64. Goldstein, L., and Murphy, D. P.: Am. J. Obst. & Gynec. **18**:189, 1929.
65. Plummer, G.: Pediatrics **10**:687, 1952.
66. Kusano, M. (chief editor): Atomic Bomb Injuries, edited by the Japanese Preparatory Committee for Le Congrès Mondial des Médecins Pour l'Étude des Conditions Actuelles de Vie, 1953, Tokyo, The Tsukiji Shokan Company.
67. Sutow, W. W., and West, E.: Am. J. Roentgenol. **74**:493, 1955.
68. Macht, S. H., and Lawrence, P. S.: Am. J. Roentgenol. **73**:442, 1955.
69. Harris, J. W. S., and Ross, I. P.: Lancet, **1**:1045, 1956.
70. Thiersch, J. B.: Am. J. Obst. & Gynec. **63**:1298, 1952.

71. Jelke, H. V.: Ann. paediat. **175**:434, 1950.
72. Davis, M. E., and Potter, E. L.: supplement to Pediatrics **19**:719, 1957.
73. Penrose, L. S.: Lancet **269**:312, 1955.
74. Takala, M. E.: Acta obst. et gynec. scandinav. **36**:28, 1957.
75. Muller, H. J.: Acta genet. (Basel) **6**:157, 1956.
76. Penrose, L. S.: Acta genet. (Basel) **6**:169, 1956.
77. National Academy of Sciences, National Research Council: Report of the Committee on Genetic Effects of Atomic Radiation, Am J. Human Genet. **8**:207, 1956.
78. Slatis, H. M.: Science **121**:816, 1955.
79. Stockard, C. R.: Am. J. Anat. **28**:115, 1921.
80. Warkany, J.: J. Pediat. **25**:476, 1944.
81. Wilson, J. G., and Warkany, J.: Am. J. Anat. **85**:113, 1949.
82. Wilson, J. G., Roth, C. B., and Warkany, J.: Am. J. Anat. **92**:189, 1953.
83. Warkany, J., and Schraffenberger, E.: J. Nutrition **27**:477, 1944.
84. Nelson, M. M.: Mammalian Fetal Development and Antimetabolites, *in* Antimetabolites, A Symposium Presented on Dec. 28-29, 1953, at the Boston meeting of the American Association for the Advancement of Science (Monograph), Washington, D. C., 1955.
85. Nelson, M. M., Baird, C. D. C., Wright, H. V., and Evans, H. M.: J. Nutrition **58**:125, 1956.
86. Giroud, A., and Boisselot, J.: Arch. franç. pédiat. **8**:648, 1951.
87. Nelson, M. M., Asling, C. W., and Evans, H. M.: J. Nutrition **48**:61, 1952.
88. Nelson, M. M., Wright, H. V., Asling, C. W., and Evans, H. M.: J. Nutrition **56**:349, 1955.
89. Boisselot, J.: Arch. franç. pédiat. **6**:225, 1949.
90. Lefebvres- Boisselot, J.: Ann. méd. **52**:225, 1951.
91. Evans, H. M., Nelson, M. M., Baird, C. D. C., and Wright, H. V.: Fed. Proc. **15**:549, 1956.
92. Thomas, B. H., Cheng, D. W.: Proc. Iowa Acad. Sciences **59**:218, 1952.
93. Gillman, J., Gilbert, C., and Gillman, T.: South African J. M. Sc. **13**:47, 1948.
94. Wilson, J. G.: Anat. Rec. **123**:313, 1955.
95. Kalter, H., and Fraser, F. C.: Genetics **37**:593, 1952.
96. Kalter, H.: Genetics **39**:185, 1954.
97. Fraser, F. C., Kalter, H., Walker, B. E., and Fainstat, T. D.: J. Cell. & Comp. Physiol. **43**:237, 1954.
98. Job, T. T., Leibold, G. J., and Fitzmaurice, H. A.: Am. J. Anat. **56**:97, 1935.
99. Warkany, J., and Schraffenberger, E.: Am. J. Roentgenol. **57**:455, 1947.
100. Wilson, J. G., and Karr, J.: Am. J. Anat. **88**:1, 1951.
101. Russell, L., and Russell, W. L.: Radiology **58**:369, 1952.
102. Hicks, S. P.: Am. J. Roentgenol. **69**:272, 1953.
103. Wilson, J. G.: J. Cell. & Comp. Physiol. **43**:11, 1954.
104. Brody, S.: Am. J. Obst. & Gynec. **64**:340, 1952.

Cor Triatriatum

Paul W. Seavey, M.D., and Edward R. Dorney, M.D.,** Emory University, Ga.*

Cor triatriatum is a rare congenital malformation. A transverse septum divides the left atrium into two separate chambers; the upper chamber receives the blood from the pulmonary veins and communicates with the lower chamber through one or more small apertures. The altered hemodynamics are identical with those of mitral stenosis, although the mitral valve is normal. The following case, diagnosed at autopsy, is presented to enhance awareness of this surgically correctable abnormality.

CASE REPORT

History.—The patient was a 5-year-old white male child who was first admitted to Emory University Hospital on April 7, 1957, for evaluation of congenital heart disease. There was no history of infectious disease in the mother during pregnancy, and delivery had been normal. Development was thought to be normal but at 1 year of age the patient became dyspneic with effort and appeared to tire easily. At age 2, he began to have brief periods of unconsciousness associated with cyanosis. No convulsive movements were described. These cyanotic episodes at first occurred 1 to 3 times per day but had gradually decreased in frequency to one episode every 2 to 3 weeks. Squatting had been noticed for the past 3 years. Dyspnea, night cough, and paroxysmal nocturnal dyspnea gradually became more pronounced.

Physical Examination.—The patient was of small stature, weighing 35 pounds. No cyanosis was noted at rest. A few petechiae were seen in the left conjunctiva. The lungs were clear to auscultation and no dullness was noted. There was prominence of the left anterior chest wall with systolic propulsion. By percussion, the heart was enlarged to the left anterior axillary line. The pulmonic second sound was very loud and split. A Grade 2 systolic murmur was heard best at the left sternal border in the third and fourth intercostal spaces. A Grade 1 diastolic runoff was heard, at first well localized in the third intercostal space, but later down the left sternal border to the apex. The liver was palpable 2 cm. below the right costal margin and the spleen was easily felt on inspiration. The electrocardiogram (Fig. 1) showed right ventricular hypertrophy and strain. Fluoroscopy and films (Fig. 2) of the chest revealed generalized cardiac enlargement and suggested a predominance of the right ventricle and right atrium. The primary and secondary pulmonary artery segments were large, but no hilar dance could be detected with the aid of the image intensifier. There was moderate pulmonary congestion.

A diagnosis was made of atypical patent ductus arteriosus with pulmonary hypertension. The patient was digitalized, placed on a low-sodium diet, and given mercurial diuretics with improvement.

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.
Received for publication July 19, 1957.
*National Heart Institute Trainee.
**Associate in Medicine.

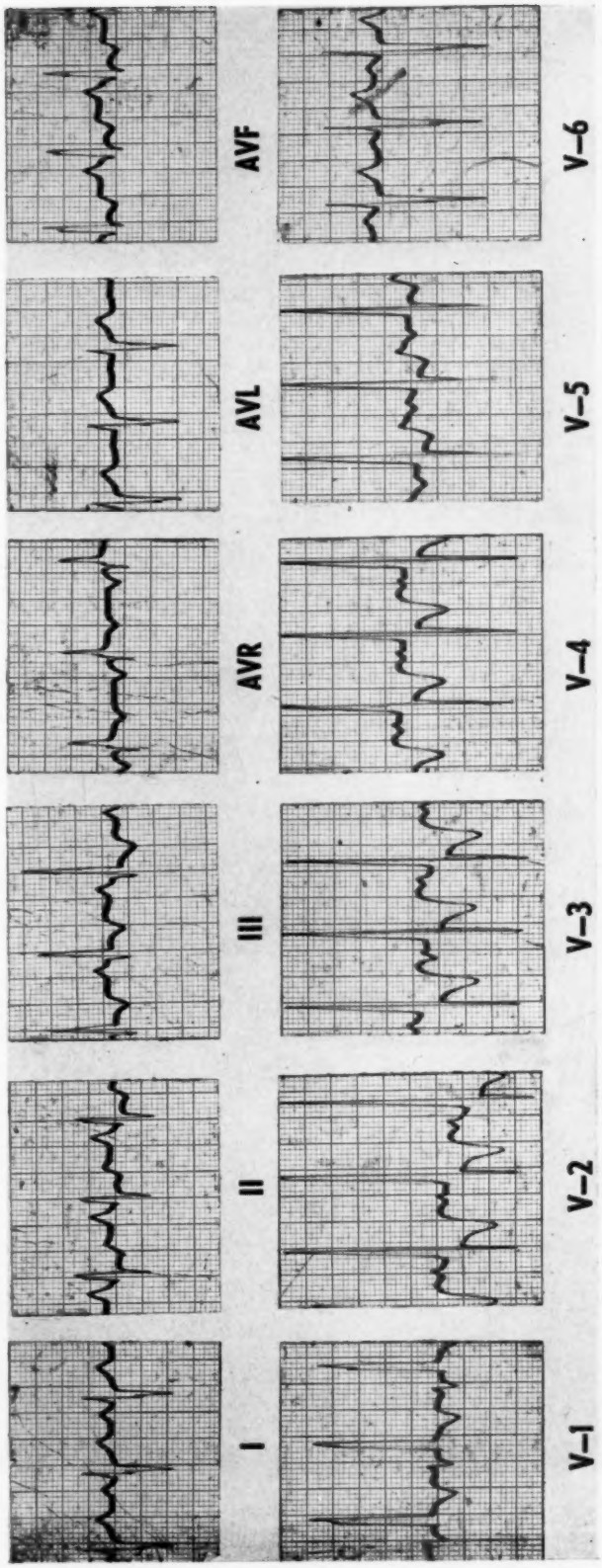


Fig. 1.—Electrocardiogram showing right ventricular hypertrophy.

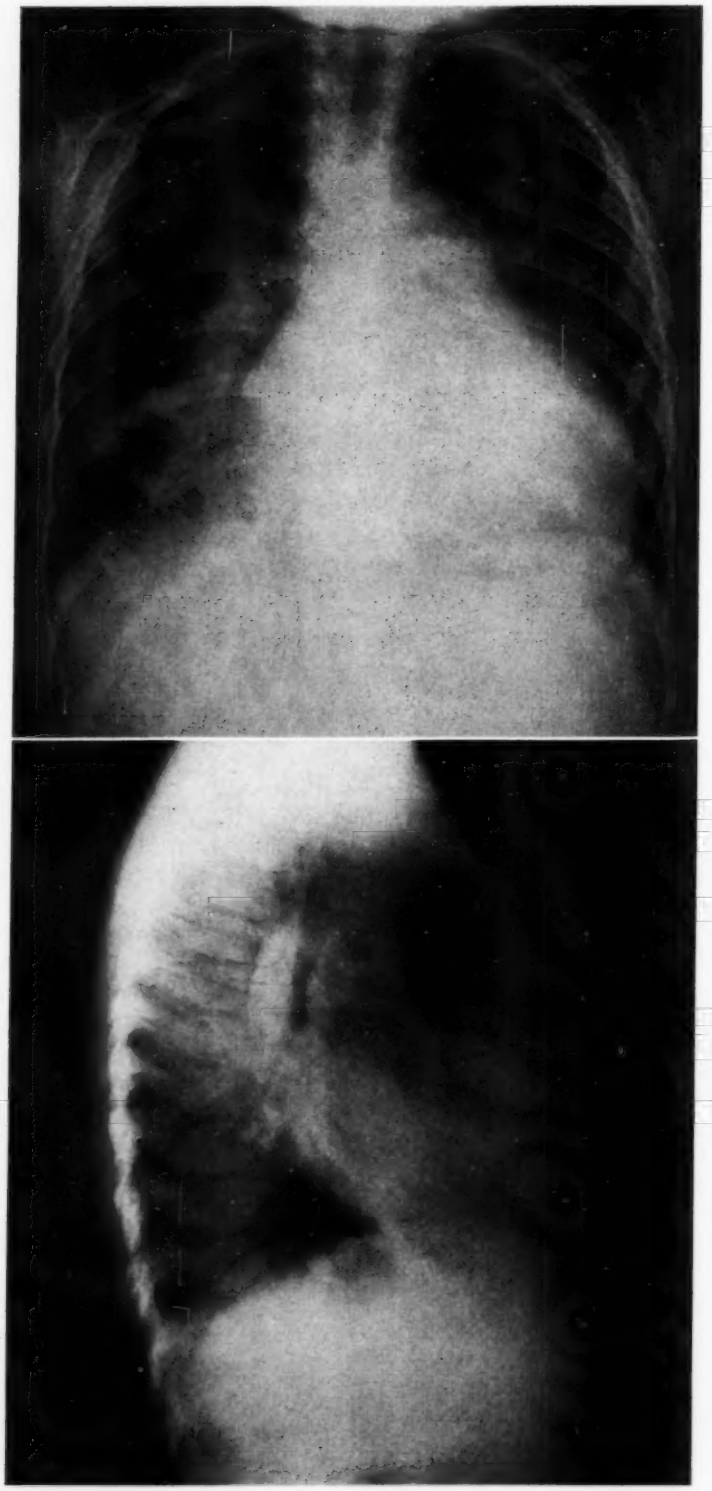


Fig. 2.—*A*, Roentgenogram of chest, posteroanterior view, showing cardiomegaly, large pulmonary artery segment, and pulmonary congestion. *B*, Left lateral view of chest.

On April 26, 1957, exploratory thoracotomy was performed by Dr. Osler A. Abbott. A patent ductus arteriosus was not present. The ligamentum arteriosus was identified, ligated, and severed. Hemosiderosis was noted in the lungs, and the pulmonary artery was considerably dilated, measuring approximately twice the diameter of the aorta. Since no obvious correctable defect could be identified, intracardiac pressures were taken and the chest was closed. In order not to complicate future surgery, pericardiotomy was not performed. The patient failed to respond and expired 5 hours after surgery was completed.

Post-Mortem Examination.—The heart weighed 260 grams. The right atrium was greatly enlarged but no endocardial lesions were noted. The foramen ovale was closed. The right ventricle was markedly hypertrophied, the wall measuring 1.5 cm. in thickness. The tricuspid and pulmonary valves were normal. The pulmonary artery was dilated but no other abnormality was noted. The pulmonary veins had a normal distribution. They opened into a cylindrical cavity measuring 3 x 1.5 cm. which was separated from the auricular appendage and mitral valve by a fibrous membrane. The only communication through this membrane was a small opening measuring 5 mm. in diameter. The mitral valve was normal. The left ventricle was small and measured 1 cm. in thickness. The aortic valve and coronary arteries were normal.

COMMENT

The embryology of cor triatriatum has been discussed thoroughly by Parsons[1] and Edwards.[2] The clinical picture is the same as that of congenital mitral stenosis[5] and may be differentiated only at surgery. About one third of the patients will have an apical systolic murmur, and occasionally a diastolic murmur has been heard. A loud first heart sound or an opening snap has never been reported. Radiographic studies usually have shown generalized cardiomegaly; however, at post-mortem examination, right ventricular enlargement is noted as well as right or left auricular hypertrophy. Cardiac catheterization studies have been reported in 2 cases and have shown elevated right atrial, right ventricular, pulmonary artery, and capillary wedge pressures indistinguishable from the findings of mitral stenosis. Angiocardiography has never been successfully carried out but should show dye retained in the left atrium similar to that of mitral stenosis. The electrocardiogram has been recorded in a few cases and has always shown marked right ventricular hypertrophy. Recently, Barrett and Hickie[3] have reported the first successful operation of a patient with cor triatriatum. This was accomplished, however, after a second thoracotomy, as the diagnosis was not entertained at the time of the first operation when a normal mitral valve was found. It should be emphasized that those patients who are operated on for mitral stenosis but who have normal mitral valves should have complete exploration of the left atrium.

SUMMARY

Cor triatriatum is a congenital defect which closely resembles congenital mitral stenosis. Apical systolic murmurs, electrocardiographic and clinical evidences of right ventricular hypertrophy, and elevated pulmonary capillary pressures are common to both entities. Roentgenographic studies may show generalized or right ventricular enlargement with pulmonary congestion but no hilar dance. At the present time differentiation of congenital mitral stenosis from cor triatriatum can be made only at surgery.

REFERENCES

1. Parsons, C. G.: Brit. Heart J. **12**:327, 1950.
2. Edwards, J. E., DuShane, J. W., Alcott, D. L., and Burchell, H. B.: A.M.A. Arch. Path. **51**:446, 1951.
3. Barrett, N. R., and Hickie, J. B.: Thorax **12**:24, 1957.
4. Pedersen, A., and Therkelsen, F.: AM. HEART J. **47**:676, 1954.
5. Braudo, J. L., Javett, S. N., Adler, D. I., and Kessel, I.: Circulation **15**:358, 1957.
6. Loeffler, E.: Arch. Path. **48**:371, 1949.
7. McLester, J. B., Bush, J. D., and DuBois, I. S.: AM. HEART J. **19**:492, 1940.
8. Barnes, C. G., and Finlay, H. V. L.: Brit. Heart J. **14**:283, 1952.
9. Cottier, Von H., and Tobler, W.: Cardiologia **30**:46, 1957.
10. Becu, L. M., Tauxe, W. N., DuShane, J. W., and Edwards, J. E., A.M.A. Arch. Path. **59**:463, 1955.
11. Hartmann, H. A.: A.M.A. Arch. Path. **59**:706, 1955.

A Modified Nylin Cardiorespiratory Test Employing a Three-Step Portable Staircase

C. Maurea, M.D., G. Nylin, M.D., F.R.C.P., and A. Sollberger, M.D.
Stockholm, Sweden

INTRODUCTION

One currently used quantitative method for estimating the cardiac function in healthy and sick persons, especially in borderline cases, consists in measuring the oxygen consumption of the subject before and after exercise of various kinds and degree, and in judging the normality of the postexercise increase of oxygen consumption, the so-called oxygen debt. This is, in effect, a combined cardiorespiratory test, but it has proved to serve well its purpose of measuring cardiac function as long as the presence of respiratory disease in the patient can be ruled out.

One cardiorespiratory test which is being used today, and concerning which a wealth of data has been accumulated in order to establish adequate normal limits, is the Nylin test. Here, the oxygen consumption is determined at rest and after a session of exercise consisting of several rounds on a specially constructed staircase (Fig. 1). The degree of exercise may be varied by suitable combinations of the number of rounds and of the pace of climbing the staircase (e.g., the notation 5/88 signifies 5 rounds at a rate of 88 steps per minute). Light signals built into the steps of the staircase set the pace for the patient and are also accompanied by the sounds of an acoustic metronome. Oxygen consumptions are determined according to Krogh.

The principle of the test is that the cardiac function of the patient shall be judged against the load to which he is constantly subjected and to which he has to adjust himself, viz., the body weight. In calculating normal values for the test, very obese cases have been excluded, since overweight may perhaps be regarded as a pathologic load as may also the increase in oxygen consumption necessary to carry the extra burden. Individual oxygen consumption values may be judged either by dotting postexercise and resting values in a normal correlation diagram or by calculating the percentual postexercise increase of oxygen consumption and comparing this value with the corresponding normal limits.

From the Cardiovascular Clinic of Södersjukhuset, Stockholm, Sweden. (Chief: G. Nylin.)
Received for publication Aug. 15, 1957.

Normal values for the tests 5/160 and 10/208 have been calculated recently by Maurea, Nylin and Sollberger[5] from a material of more than 600 normal cases. The physiologic mechanism of the test has been investigated by Hesser and Nylin.[2] Among other things it was shown that the exercise performed in descending the staircase amounts to about 1/5 of that performed in ascending the staircase.

Fig. 1.—The specially constructed large staircase.

One drawback of this test is the size and construction of the staircase. Only the bigger and more specialized clinics can afford to use it. On the other hand, the oxygen determinations may be performed anywhere, since they are used for other purposes as well, e.g., in determining the basal metabolism.

Certainly the usefulness of the test would increase if a small portable staircase could be substituted for the original one. In that case, however, it would have to be determined whether the two tests were comparable at all, how many rounds in the small staircase were mechanically equivalent to one round in the big one, and whether the normal values stated for the original test were applicable to the new one.

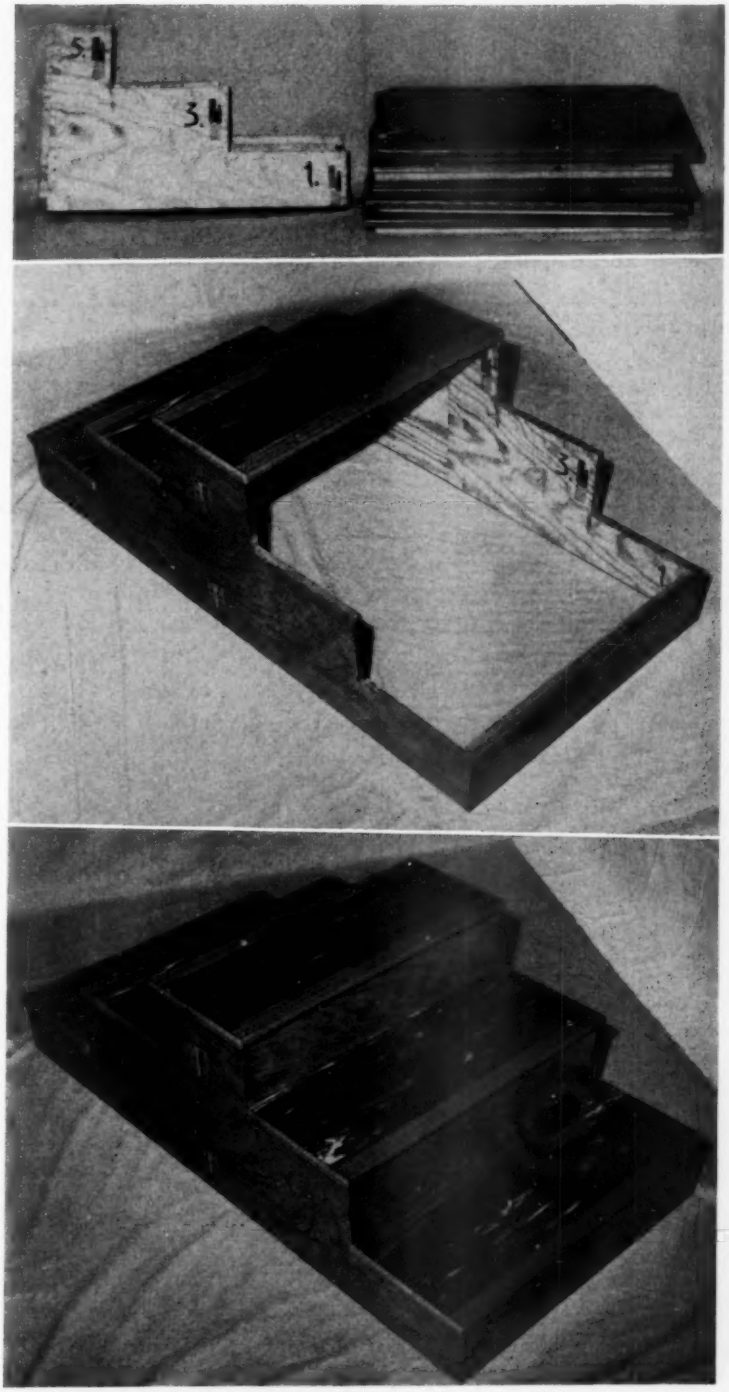


Fig. 2.—The simple three-step small staircase.

For this purpose a simple three-step staircase, exactly half a meter high, was built. It is simple to build and may readily be taken apart or reassembled, being easy therefore to store or to move from place to place. In Fig. 2 it is shown in dismantled and in reassembled state, and in Fig. 3 the technical data are given.

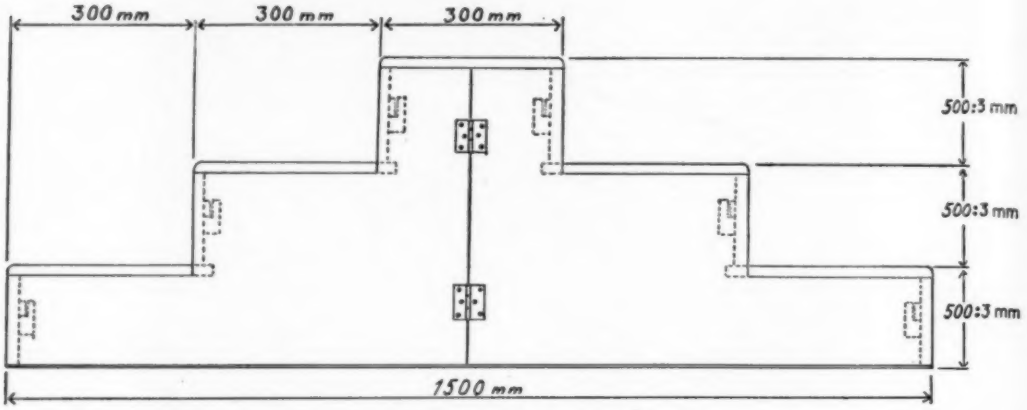


Fig. 3.—Design drawing of the small staircase.

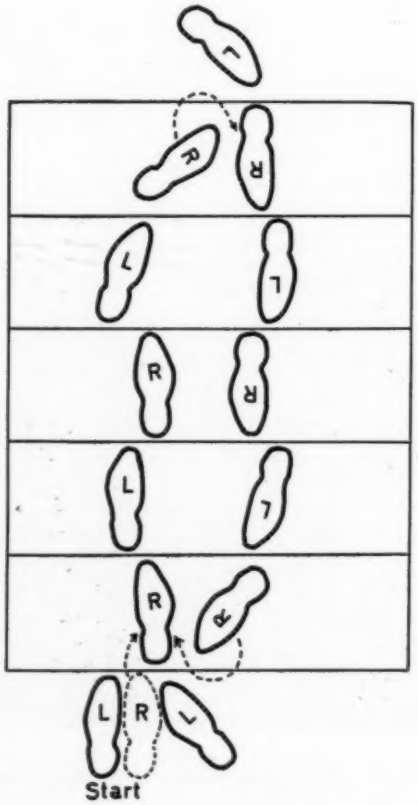


Fig. 4.—Performance of steps on the small staircase.

The subject is directed to run on the staircase as indicated in Fig. 4. He is constantly turning in one direction and is trying to adjust his pace to that of an ordinary metronome. Four complete rounds on the small staircase correspond, mechanically, to one complete round on the large one.

Small staircases of this kind have been used for different purposes on many occasions. Master[3,4] and Riseman,[7] for example, use a two-step staircase for obtaining the exercise ECG. The patient performs a number of rounds which is determined by his age and body weight. In Sweden the test has been tried by Hallström.[1]

The present study presents a modified and simplified Nylin cardiorespiratory test which may be used in any laboratory, and which purports to compare the values obtained with this and with the original test as regards the three exercises 5/88, 5/160, and 10/160 in healthy and sick subjects.

MATERIAL AND METHODS

Fifty-one double tests (big and small staircase) were performed from Sept. 18 to Oct. 9, 1956, with 22 healthy subjects and 9 persons suffering from cardiovascular disease. The healthy subjects belonged mainly to the staff, and included Swedes, Germans, and Italians, all without any demonstrable signs of disease. The pathologic cases were obtained from the Heart Clinic. The material included 15 men and 16 women. In all, nineteen 5/88 double tests were performed,

TABLE I

	HEALTHY MEN (10 CASES)	HEALTHY WOMEN (12 CASES)	PATHOLOGIC CASES (5 MEN AND 4 WOMEN)
Age (years)	28.3 ± 2.0 6.3 (18—37)	33.8 ± 2.8 9.8 (22—54)	53.1 ± 2.6 7.8 (44—64)
Body weight (Kg.)	70.8 ± 2.4 7.8 (59—81)	58.2 ± 1.8 6.3 (48—68)	69.1 ± 4.2 12.7 (55—92)
Body surface ($M.^2$)	1.86 ± 0.04 0.12 (1.7—2.0)	1.63 ± 0.03 0.10 (1.5—1.8)	1.77 ± 0.06 0.19 (1.5—2.1)
O_2 consumption at rest (c.c./min.)	251 ± 6.2 19.6 (217—276)	198 ± 4.8 16.6 (171—235)	223 ± 11.6 34.9 (179—286)
Basal metabolic rate (%)	+0.33 ± 1.62 5.11 (−5—+12)	+0.81 ± 2.44 8.45 (−12—+14)	+6.56 ± 3.68 11.04 (−4—+27)
Heart volume (absolute, c.c.)			1,080 ± 107 322 (670—1,640)
Heart volume (relative, $c.c./M.^2$)			609 ± 66 197 (350—930)

The values are: mean ± error of mean, standard deviation. Range in parentheses.

sixteen 5/160 tests, and sixteen 10/160 tests. All three tests were tried in 5 subjects. The healthy persons were submitted to 41 tests, the pathologic cases to 10 tests. The characteristics of the material are recorded in Table I.

The age of the healthy subjects varied from 18 to 54 years, the mean age for the two sexes differing but little. The pathologic cases were considerably older, from 44 to 64 years. The basal metabolic rate values were normal, except in 2 pathologic cases where they exceeded +15 per cent. The heart volume of the pathologic cases exceeded the normal limits in several instances. The clinical diagnoses were: aortic stenosis, cardiosclerosis plus presenility, mitral stenosis, angina pectoris, collagenosis plus cardiac enlargement, angina pectoris plus obesitas, traumatic heart injury, and exercise dyspnea.

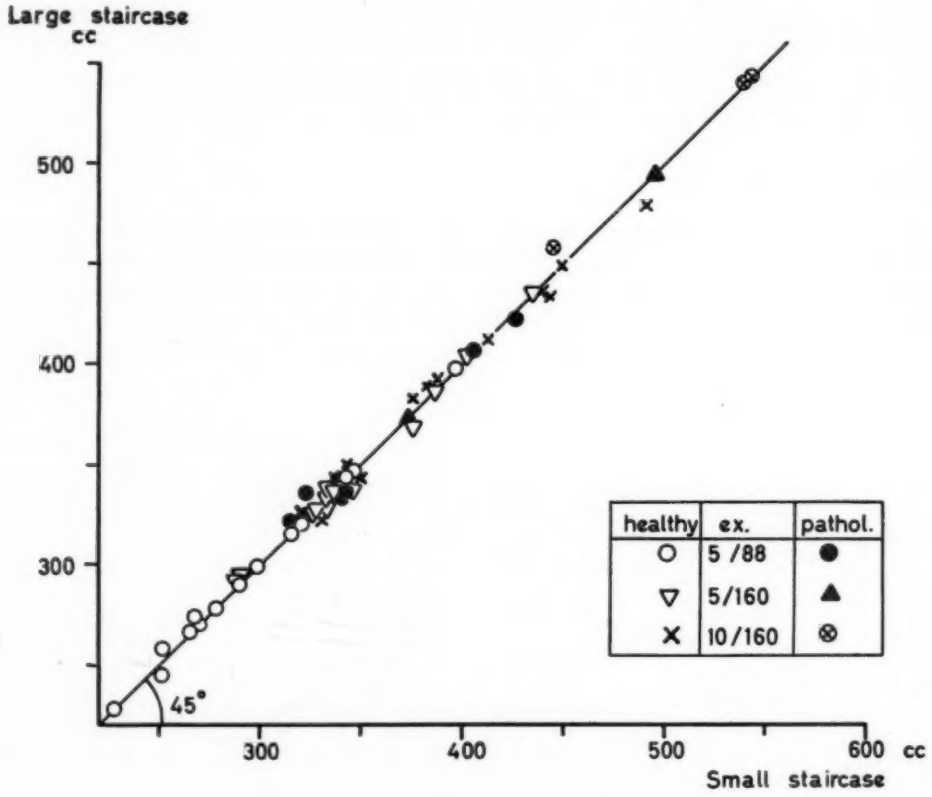


Fig. 5.—Correlation between O_2 consumptions after exercise on the two staircases.

The Nylin cardiorespiratory test and the large and small staircases have already been described. One double test comprises recordings after exercise on both staircases. In every second double test the subject climbed the large staircase first, and in the intervening double tests the small one first. Between the two component tests he rested for about half an hour. The exercises tried were: 5(20)/88, 5(20)/160, and 10(40)/160. The first figure gives the number of rounds on the large staircase, the number in parentheses those on the small one. The oxygen consumption was measured before each double test and from the beginning of the second to the end of the fifth minute after each component exercise test.

The oxygen consumptions at rest and the basal metabolic rate values were given together with the other characteristics of the material. The oxygen consumptions after exercise on the large staircase and the absolute and percentual oxygen debts calculated therefrom will be given later. The values recorded after exercise on the large and on the small staircase will be compared inter se.

RESULTS

The 51 pairs of oxygen consumption values obtained after exercise on the large and on the small staircase have been plotted in Fig. 5. They seem to agree very closely. The mean difference (small staircase minus large staircase values) was $+0.25 \pm 0.63$ c.c. or 0.07 per cent. The mean difference is not significant; there is no tendency for either value to be larger. Hence, a tentative over-all error of method for the test may be calculated from the standard deviation of the differences ($\sigma_D = 4.52$ c.c.) according to the method of double determinations (error of method $= \sigma_D/\sqrt{2}$). The error is 3.2 c.c. or 0.9 per cent. The largest individual differences were -11 and $+11$ c.c., respectively.

All the oxygen consumptions were calculated from the Krogh curves by the same investigators (two persons). Hence, a certain bias towards the equalization of large and small staircase values may, perhaps, not be entirely possible to avoid.

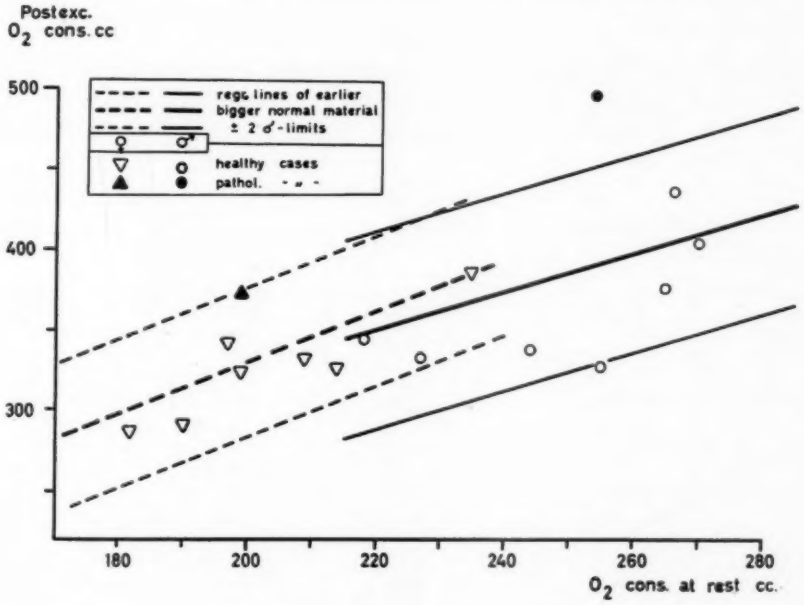


Fig. 6.—Correlation between postexercise and resting O_2 consumption as compared with earlier normal limits. Exercise 5/160.

However, the persons in question had extensive training in the procedure and, even if a considerable bias is allowed for, the differences between large and small staircase values must still be considered very small as compared with the absolute magnitude of the oxygen consumptions recorded.

Obviously the modified Nylin test may be used without difficulty and the results obtained may be compared with the normal values stated for the original test.

Postexercise O_2 consumptions, absolute and percentual debts for healthy men and women and for pathologic cases for each of the exercises tried are given in Table II.

The values increase with increasing exercise. Men generally present higher values than women, except in the case of the percentual debt, where the reverse seems to apply. Pathologic cases have higher values than the normal ones.

The values for exercises 5/88 and 10/160 may be used in establishing normal limits, although the number of cases is, of course, rather small. The upper normal limits for the percentual debt(2σ limits) then would be tentatively as shown in Table III.

In the case of exercise 5/160, a large normal series has been reported earlier, the upper normal limits of the percentual debt being for men 79 per cent and for women 83 per cent. The values found in this study generally agree with those limits. The values given for exercises 5/88 and 10/160 have no earlier counterparts and may be used until larger series are available.

In Fig. 6 the postexercise and pre-exercise oxygen consumption values of exercise 5/160 (large staircase) have been plotted against each other and against

TABLE II

	EXERCISE TEST	HEALTHY MEN	HEALTHY WOMEN	PATHOLOGIC CASES
O_2 consumption after exercise (c.c./min.)	5/88	340 ± 16.6 229—397 37.4 (5)	269 ± 9.0 224—320 26.9 (9)	362 ± 22.6 320—421 50.5 (5)
	5/160	365 ± 15.7 326—435 41.6 (7)	327 ± 12.6 287—386 33.3 (7)	435 ± 373—496 — (2)
	10/160	411 ± 21.3 343—490 56.4 (7)	344 ± 18.7 287—412 45.8 (6)	509 ± 445—542 — (3)
Absolute O_2 debt (c.c./min.)	5/88	86.6 ± 5.5 77—109 12.4 (5)	70.2 ± 3.4 53—85 10.3 (9)	153.0 ± 11.7 115—178 26.1 (5)
	5/160	115.3 ± 11.8 71—169 31.3 (7)	123.3 ± 6.8 101—151 18.1 (7)	208.5 ± 175—242 — (2)
	10/160	159.7 ± 15.3 88—224 43.3 (7)	139.5 ± 11.4 105—178 27.8 (6)	272.0 ± 247—316 — (3)
Debt, in per cent of resting value	5/88	34.6 ± 2.1 29—40 4.8 (5)	35.3 ± 1.0 31—41 3.0 (9)	73.2 ± 4.1 58—80 9.2 (5)
	5/160	48.0 ± 3.7 39—64 9.9 (7)	60.7 ± 2.7 53—74 7.3 (7)	92.0 ± 89—95 — (2)
	10/160	64.9 ± 4.3 46—84 11.5 (7)	67.8 ± 3.5 58—79 8.5 (6)	118.0 ± 89—140 — (3)

The values are: mean ± error of mean, range, standard deviation, with number of cases in parentheses.

the normal regression and $\pm 2\sigma$ limits found in the earlier presentation of normal values. Separate normal limits were given for men and for women. The present values of the healthy subjects seem to agree with these limits. One of the pathologic cases displays definitely non-normal values.

The corresponding correlations for exercises 5/88 and 10/160 (large staircase) have been plotted in Figs. 7 and 8. The correlations are good as regards the women, probably owing to the smaller variation of these values as compared with those for the men. In most cases the pathologic values differ very obviously from the normal. Correlations were also calculated for the healthy cases and are shown in Table IV.

For exercises 5/88 and 10/160 the regression lines given above have been drawn in Figs. 7 and 8, together with the $\pm 2\sigma$ limits.

Thus, the normality of individual pairs of values may be judged by dotting them into the diagrams and by judging the position of the point as compared to the normal limits. In applying the latter limits, however, one should not forget that the material is, as yet, quite small. Here correlations have been given in terms of the big staircase values. Obviously, they apply also to values obtained by use of the small staircase, the modified Nylin cardiorespiratory test.

TABLE III

	5(20)/88	5(20)/160	10(40)/160
Men	44%	67%	88%
Women	41%	75%	84%

TABLE IV

EXERCISE	MEN	WOMEN
5/88	0.96 ± 0.04^{x} $y = 1.20x + 35.0$ 12.5 (5)	0.98 ± 0.01^{xxx} $y = 1.51x - 30.5$ 5.6 (9)
5/160	$0.69 \pm 0.20^{-}$ $y = 1.40x + 16.6$ 33.1 (7)	0.90 ± 0.07^{xx} $y = 1.71x - 21.0$ 15.8 (7)
10/160	$0.74 \pm 0.17^{-}$ $y = 1.99x - 89.4$ 41.6 (7)	0.96 ± 0.08^{xx} $y = 2.28x - 122.3$ 14.4 (6)

The values are: coefficient of correlation ± error, regression line, standard deviation around regression line, with the number of cases given in parentheses.

Postexercise oxygen consumption values = y; resting values = x.

Statistical significances are stated according to the following definitions:

$0.05 > P \geq 0.01$ x probably significant
$0.01 > P \geq 0.001$ xx significant
$P < 0.001$ xxx highly significant

It would seem reasonable also to assume that the modified and the original tests may agree equally well for exercises other than those tried here. In heavier tests, however, the number of turns on the small staircase tends to become too great and the subjects get giddy.

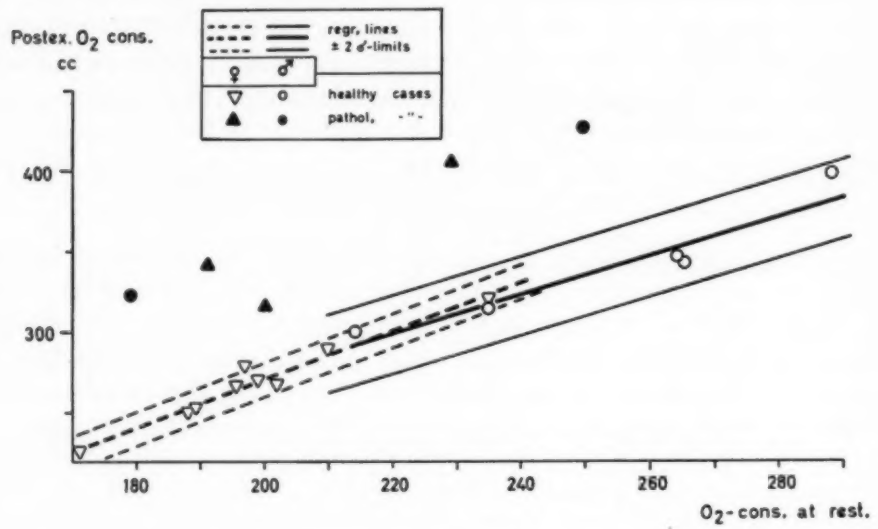


Fig. 7.—Correlation between postexercise and resting O_2 consumptions after exercise 5/88.

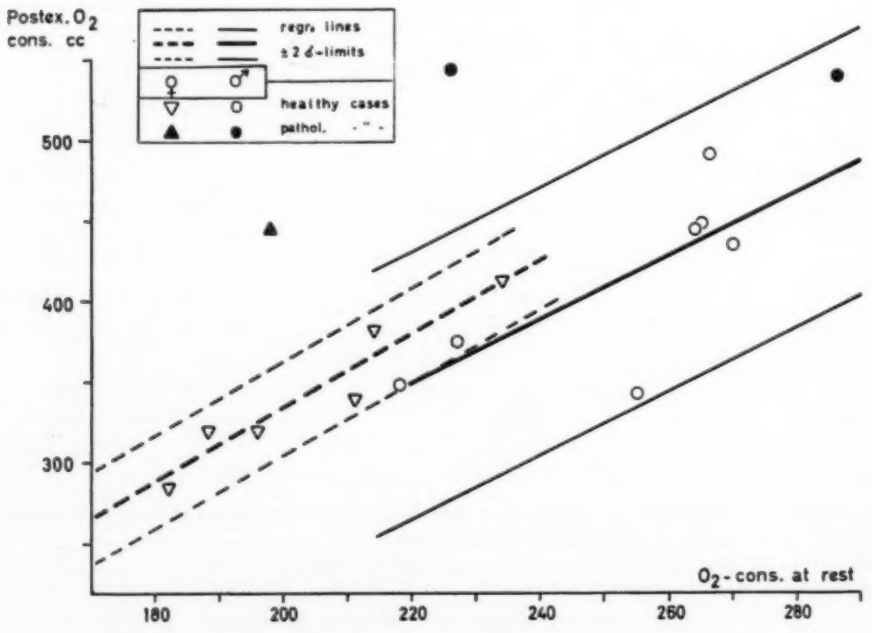


Fig. 8.—Correlation between postexercise and resting O_2 consumptions after exercise 10/160.

The staircase, of course, may be used also for other purposes simultaneously, e.g., for obtaining exercise electrocardiograms according to Master. In that case mechanical equivalents between the number of rounds used in the Master two-step staircase and the present one will have to be calculated.

SUMMARY

1. A simplified Nylin cardiorespiratory test is presented. A small, easily made and portable staircase is substituted for the larger one ordinarily used. The step rate is set by an ordinary metronome. Four rounds on the small staircase are mechanically equivalent to one round on the large one. Oxygen consumptions were recorded with the Krogh apparatus before and after exercise.

2. Fifty-one double tests were performed with 22 healthy subjects and 9 pathologic cases (15 men and 16 women). One double test includes the recording of O_2 consumptions before exercise and after exercise on both staircases, about half an hour elapsing between the two rounds in the latter case. Three different exercises were tried, 5(20)/88, 5(20)/160, and 10(40)/160; 5(20)/88 signifies 5 rounds on the big staircase or 20 rounds on the small one at a pace of 88 steps per minute.

3. The values obtained with the small and the big staircases do not differ significantly and the differences are numerically very small. The mean difference was 0.25 ± 0.63 c.c. or 0.07 per cent. The highest difference was 11 c.c. Thus, both tests may be used indiscriminately, and the normal values reported earlier for exercise 5/160 on the larger staircase may be applied in judging values obtained with the small staircase.

4. Normal values for the test 5/160 have been given earlier. As regards exercises 5/88 and 10/160, however, the present values may be used until larger series have been accumulated. The upper normal limit would then be: for men, 5/88—44 per cent, 10/160—88 per cent; and for women, 5/88—41 per cent, 10/160—84 per cent.

5. The post- and pre-exercise O_2 consumptions are positively correlated. Regression lines and 2σ limits for the normal cases have been indicated in Figs. 7 and 8.

REFERENCES

1. Hallström, L.: Svenska Läkartidn. **48**:464, 1951.
2. Hesser, C. M., and Nylin, G.: Physiological Aspects on the Nylin Cardio-Pulmonary Function Test, Second European Congress of Cardiology, Sept. 10-14, 1956.
3. Master, A. M.: M. Clin. North America **34**:705, 1950.
4. Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C., Jr.: Am. J. Med. Sc. **207**:435, 1944.
5. Maurea, C., Nylin, G., and Sollberger, A.: Acta Cardiologica **10**:336, 1955; **11**:215, 1956; Normal Values of Nylin's Cardio-Respiratory Function Test, Second European Congress of Cardiology, Sept. 10-14, 1956; Il Volume Cardiaco Normale, Reports of the 17th Congr. Soc. Ital. Card., Chianciano, May 1955; Valori normali del test funzionale cardio-respiratorio di Nylin, Reports of the 18th Congr. Soc. Ital. Card., Trieste, May 1956.
6. Nylin, G.: Acta med. scandinav., suppl. 52, 1933; suppl. 92, 1938.
7. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: Am. Heart J. **19**:683, 1940.
8. Sutton, G. C., Swisher, W. P., and Sutton, D. C.: Am. Heart J. **53**:171, 1957.

Hemodynamic Complications in Tetralogy of Fallot After Pulmonary Valvectomy or Infundibulectomy (Brock Procedure)

T. K. Lin, M.D., Antoni M. Diehl, M.D., and C. Frederick Kittle, M.D.
Kansas City, Kans.

The ultimate goal in treatment of the tetralogy of Fallot is correction o the basic anatomic defects and establishment of normal cardiophysiologic func tion. The creation of an aortopulmonic communication suggested by Blaloc and Taussig[1] and Potts[2] usually results in improved cardiophysiologic functio Relief of the pulmonary stenosis by valvotomy or infundibular resection as pro posed and subsequently reported by Brock, Campbell and associates[3-5] correct one of the anatomic defects. In a group of 25 patients with Fallot's tetralog operated upon at the University of Kansas Medical Center by pulmonary va vectomy or infundibulectomy, 3 individuals have had serious postoperative hemo dynamic complications. The present communication reports these in detail an their physiologic explanation.

METHODS AND MATERIALS

The usual technique of catheterization of the right side of the heart was carried out after hours of fasting. The mid-chest level was used as a reference point for blood pressure measur ments. The blood pressure tracings were recorded using Statham P23D strain gauges and Sanborn Poly-Viso direct writer. The oxygen consumption was measured by a Collin's chai compensated gasometer (Serial No. 849) in the preoperative and postoperative studies on Case as well as in the postoperative study on Case 1. Oxygen content of the blood samples was d termined by the Van Slyke-Neill method.[6] The respiratory gas determinations were carried o utilizing the Beckman oxygen analyzer (Model C, Serial No. 324). Cases 1 and 3 were studi under local procaine anesthesia and Case 2 was under rectal Avertin anesthesia. The PF/S ratio was derived from the following formula based on Fick's principle:

$$\frac{PF}{SF} = \left[\frac{O_2 \text{ consumption (c.c./min.)}}{\text{Pulm. vein—Pulm. art. } O_2 \text{ content (vol. \%)}}\right] \div \left[\frac{O_2 \text{ consumption (c.c./min.)}}{\text{Femoral art.—mixed venous blood } O_2 \text{ content (vol. \%)}}\right] = \frac{\text{Femoral art.} - \text{mixed venous blood } O_2 \text{ conte}}{\text{Pulm. vein—Pulm. art. } O_2 \text{ content}}$$

From the formula, a cancellation of oxygen consumption is noted.

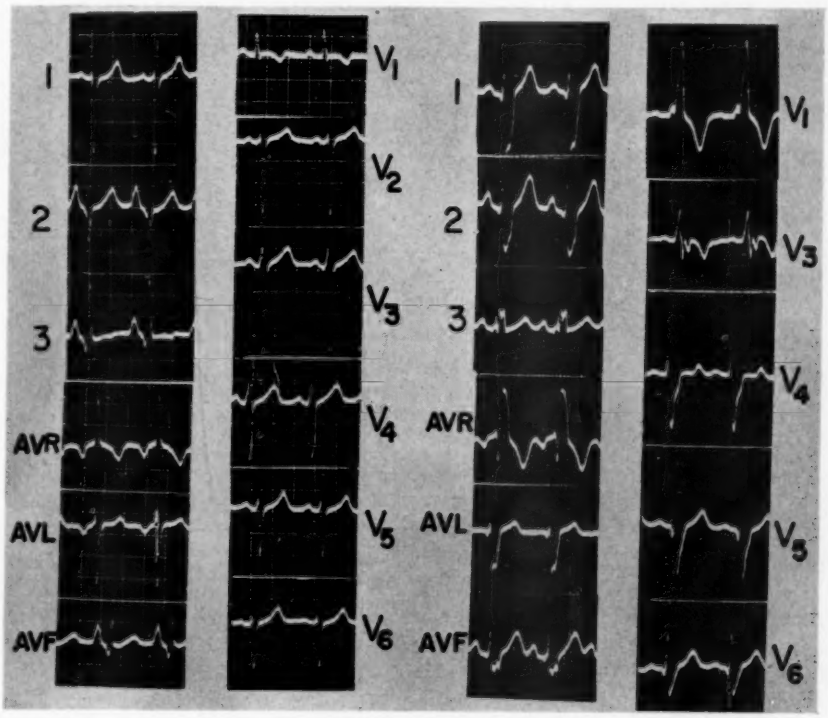
From the Departments of Medicine, Pediatrics, and Surgery of the University of Kansas School Medicine, Kansas City, Kans.

This study is supported in part by the Kansas Heart Association.

Received for publication Aug. 15, 1957.

CASE REPORTS

CASE 1.—L. S., a 22-year-old male, was noted to have cyanosis beginning at 10 months of age. He had some decrease in his exercise tolerance throughout childhood, and was able to walk one flight of stairs or 3 to 4 blocks without severe dyspnea when seen initially at the University of Kansas Medical Center on Sept. 19, 1951. Physical examination showed a diffusely cyanotic young man whose weight was 134 pounds and height 69 inches. The peripheral pulses were all normal. The heart was not enlarged to percussion, but a heave was present over the anterior chest wall. The second sound over the pulmonary area was diminished in intensity and less than the aortic second sound. A blowing, apical, Grade 2 systolic murmur was present. The electrocardiogram showed right ventricular and auricular hypertrophy (Fig. 1). Cardiac fluoroscopy revealed the heart to be slightly increased in its transverse diameter with enlargement of the right ventricle and diminution in the peripheral pulmonary vascularity. A roentgenogram corroborated these findings (Fig. 2).



A. *B.*

Fig. 1.—Case 1. Developed right bundle branch block after infundibular resection, with increased amplitude of R wave at V_6. *A*, Before operation (9-20-51). *B*, One year after infundibular resection (6-11-55).

Preoperative right heart catheterization (Table I) showed the following pertinent findings: (1) pulmonary stenosis as noted by a marked systolic pressure gradient between the right ventricle and the main pulmonary artery, (2) evidence of a "common ventricle" as indicated by essentially identical systolic pressures in the right ventricle and the femoral artery, (3) evidence of a right-to-left shunt by arterial oxygen desaturation in the femoral artery. There was marked polycythemia with a hemoglobin of 24.3 Gm. per cent and a red blood cell count at 9,250,000. Operation was not advised at this time. He was seen again on Jan. 15, 1953, when it was believed that he would benefit from a pulmonary valvotomy. On Jan. 19, 1953, thoracotomy was carried out, revealing an enlargement of the right ventricle and a narrowed, flabby pulmonary artery. The latter vessel measured 1.5 to 2 cm. in diameter. The aorta appeared normal. An infundibular chamber was

TABLE I

NAME SEX AGE (YR.)	DATE	PRESSURE (MM. Hg) SYSTOLIC/DIASTOLIC (MEAN)							FA O_2 CON. (VOL. %) O_2 SAT. (%)	O_2 CAP. (VOL. %)	OXYGEN CONTENT (VOL. %)							
		RA	RV	PA	PAW	AORTA	FA	LV			SVC	IVC	RA	RV	PA	PAW	CS	PF/SF RATIO
Case 1 L.S. M	Preop. 10/18/51		110/10	25/12 (15)	(7)		120/90‡		27.3 82.6%		23.1			24.2	24.3			0.42
22	Postop. 6/13/55	12/0 (6)	120/8 68/5*	45/5 (25)			120/80‡		20.4 93.1%	21.75	13.1			15.2	17.9			1.44
Case 2 C.C. F	Preop. 8/26/54	7/2 (3)	95/5†	(5)		70/50†	90/80‡		18.7 70%	27.2	14.1		13.1	15.8	16.5			0.58
8	Postop. 6/16/55	20/10 (18)	87/20 (40)	80/20 (35)	(18)	90/65	110/70 (85)	90/13	17.4 85%	20.13	13.9	12.1	12.6	15.9	15.8	18.9	2.5	1.18
Case 3 D.T.	Preop. 2/9/56	10/2 (4)	132/10 (55)	17/7 (10)	(1)		120/80 (68)		24.2 85.9%	28.44	20.1	19.8	19.1	20.5	20.9			0.54
M 19	Postop. 4/9/56	18/3 (8)	125/12 (50)	52/8 (34)			120/80 (68)		21.6 95.6%	22.82	14.1	14.8	14.48	17.10	16.96			1.54

*Infundibular chamber.

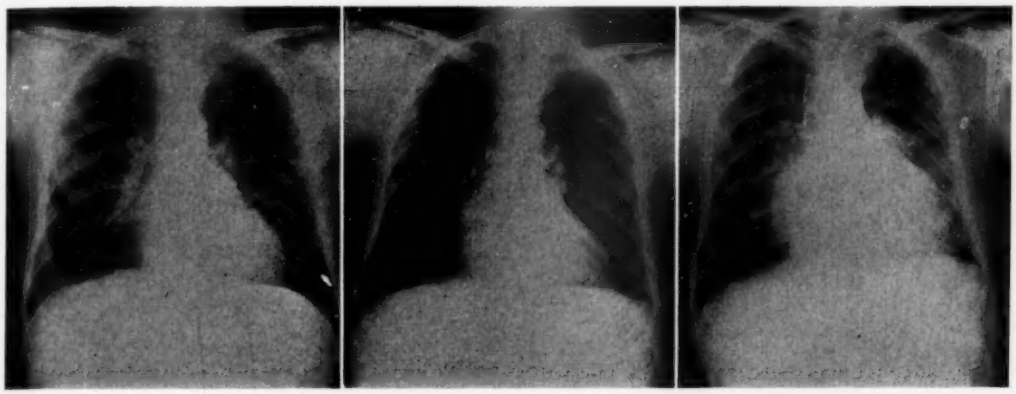
†Aortic and right ventricular pressures were recorded at different times.

‡Taken by regular sphygmomanometer.

RA = right auricle; RV = right ventricle; PA = pulmonary artery; PAW = pulmonary artery wedge; FA = femoral artery; LV = left ventricle; SVC = superior vena cava; IVC = inferior vena cava; CS = coronary sinus; PF = pulmonary flow; SF = systemic flow.

present proximal to the pulmonary valve, measuring about 6 by 5 cm. in its diameters. A systolic thrill was palpable over this chamber and in the pulmonary artery. A Brock pulmonary valvulotome, the smaller size, and then the larger size, was inserted through the right ventricle, incising the infundibular stenosis in several axes, and into the pulmonary artery. The area of stenosis was thought to be at this time some 15 to 18 mm. in diameter. No tissue was removed.

The postoperative course was not unusual. There was considerable visible diminution in the cyanosis following the operative procedure. However, this did not persist. He was discharged 3 weeks postoperatively and was readmitted on May 30, 1954, complaining of tiredness since December, 1953, and a decrease in his tolerance for exercise approaching that observed preoperatively. A roentgenogram of the chest taken 16 months after infundibulotomy is shown in Fig. 2.



A. *B.* *C.*

Fig. 2.—Case 1. L. S., male, 22 years old. Shows progressive cardiac enlargement and accentuation of pulmonary vascular markings. *A*, Before infundibulotomy. *B*, Sixteen months after infundibulotomy. *C*, One year after partial infundibulectomy.

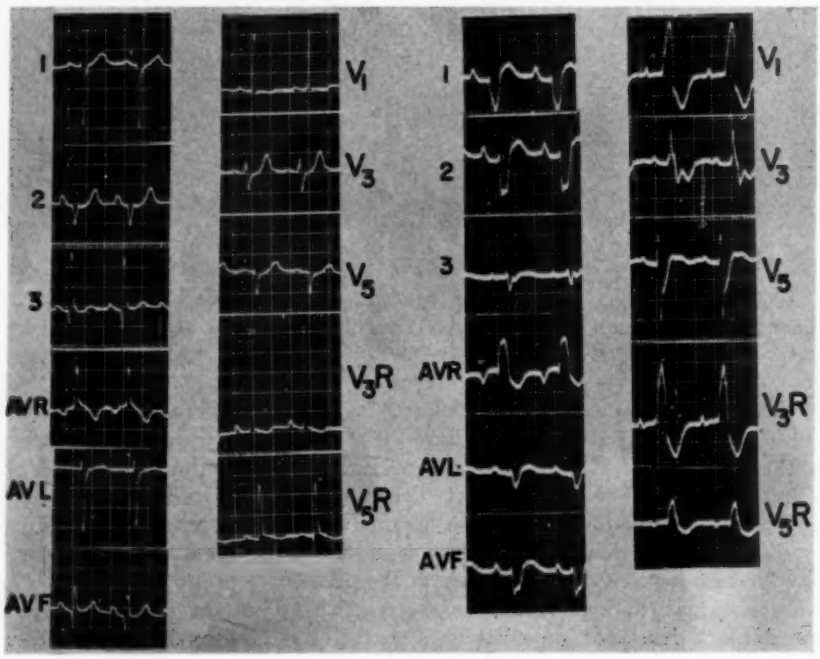
Because of the increased cyanosis and limited activity tolerance, thoracotomy was advised again and done on June 16, 1954. Palpation of the heart at this time revealed a well-localized, jet-like thrill over the infundibular chamber and the pulmonary artery; the latter vessel was slightly dilated down to its base. The right ventricle was still enlarged. Utilizing a transventricular approach and the Brock infundibular punch, a number of pieces of fibrous tissue and myocardium were removed from the localized, infundibular stenosis. It was felt that the procedure caused a considerable increase in the systolic pressure in the pulmonary artery. It was now possible for the surgeon to pass his fifth finger from the right ventricle up into the pulmonary artery. A right bundle branch block developed immediately after the infundibular resection and persisted postoperatively.

Postoperatively, considerable hemorrhage occurred into the chest, requiring re-exploration and ligation of several pleural vessels. Because of cardiomegaly and mild right heart failure following this second Brock procedure, right heart catheterization was repeated postoperatively on Aug. 26, 1954, with the following findings as compared to the preoperative study: (1) a rise of the pulmonary artery pressure, (2) presence of a pulmonary valvular and infundibular stenosis as indicated by a pressure of 45/5 mm. Hg in the pulmonary artery and 68/5 mm. Hg in the infundibular chamber, (3) an increase of the peripheral oxygen saturation in the femoral artery, and (4) reversal of the ventricular shunt, now being left to right instead of right to left.

He was seen again on Dec. 3, 1954. There was gradual improvement in his tolerance for exercise and decrease in the cyanosis. A Grade 4, prolonged systolic murmur with a Grade 1 to 2 systolic thrill and a Grade 1 decrescendo diastolic blow were evident over the pulmonary area. The pulse rate was 90 per minute and his blood pressure 150/100 mm. Hg. Moderate cardiac enlargement remained (Fig. 2). The findings in June, 1955, almost one year after infundibular resection, were essentially the same. An electrocardiogram at this time is shown in Fig. 1.

Comment: This is a case of Fallot's tetralogy with infundibular, and probably pulmonary, valvular stenosis. After infundibular resection, significant cardiac enlargement developed, and moderate left-to-right shunt as well as pulmonary regurgitation and right bundle branch block were evident. Subjective improvement of his tolerance for exercise was noted even in the presence of cardiomegaly.

CASE 2.—C. C., an 8-year-old girl, was first seen for evaluation in August, 1954. The mother, a rather poor informant, stated that the girl was well until 1 year of age, when she suffered a fall, striking her head on the pavement. Following this she had paralysis of the left side and it was thought that she had a "brain clot." Residual hemiparesis persisted. Since 1 year of age she was noted to be cyanotic, with an increasing degree of the cyanosis in the last year. The cyanotic episodes were noted to be more severe upon exertion or crying and she would sit down frequently to catch her breath, but there was no definite squatting. Because of the paralysis on the left side, it was difficult to evaluate her tolerance for exercise.



A. *B.*

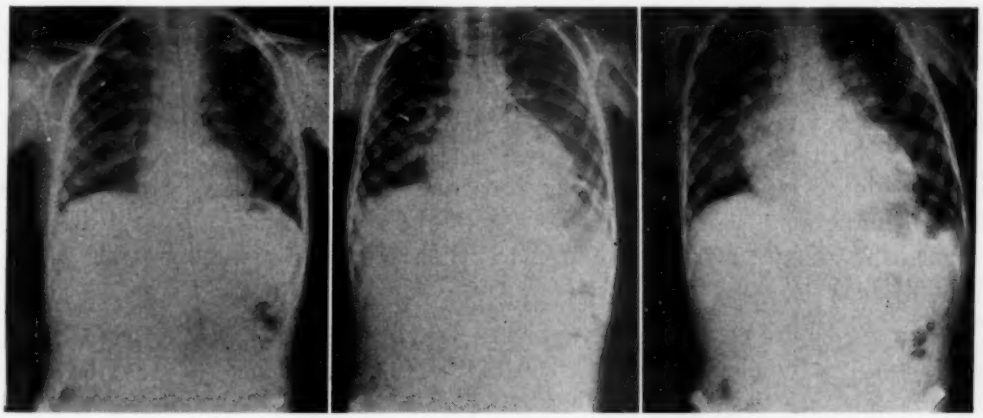
Fig. 3.—Case 2. Developed postoperative right bundle branch block. *A*, Before operation (8-25-54). *B*, Nine months after infundibular resection (6-15-55).

Physical examination showed a moderately cyanotic girl with left hemiplegia. The blood pressure was approximately 90/80 mm. Hg in the right arm. Her height was 46.5 inches and weight, 39 pounds. A short, Grade 3 systolic murmur was noted at the left sternal border in the third interspace. The second pulmonic sound was slightly accentuated and greater than the second aortic sound. The electrocardiogram showed right ventricular hypertrophy (Fig. 3). A roentgenogram of the heart (Fig. 4) showed it to be within normal limits in its transverse diameter. There was some concavity of the left mid-border of the cardiac silhouette. The vascularity in the hilar regions was slightly diminished, as well as in the peripheral lung fields. The impression at this time was cyanotic congenital heart disease, probably tetralogy of Fallot. Because of the severity of the cyanosis and apparent incapacity, right heart catheterization (Table I) was carried

out with the following findings: (1) pulmonary stenosis as noted by a marked systolic pressure gradient between the right ventricle and the pulmonary artery, (2) evidence of a "common ventricle" as indicated by essentially identical systolic pressures in the right ventricle and aorta, and (3) evidence of a right-to-left shunt as presented by a marked peripheral oxygen desaturation in the femoral artery.

On Sept. 4, 1954, with the patient under endotracheal anesthesia, a left thoracotomy incision was made and the heart exposed. An infundibular type of pulmonic stenosis was observed. A Pott's valvulotome and subsequently a Brock infundibulotome were passed through the stenosis using a right ventriculotomy. Twelve fragments of fibrous and myocardial tissue were removed from the infundibular area. This was followed by a noticeable increase in the size of the previously small pulmonary artery and a decrease in the thrill over the area. The systolic pressure tracings taken from the pulmonary artery and the right ventricle showed no essential change in the latter, but there was an increase in the former, from 7 mm. Hg before infundibulectomy to 24 mm. Hg afterward.

On the fourth postoperative day signs of decompensation of both left and right ventricles became evident as manifested by tachypnea, right pleural effusion, and hepatomegaly. Her management consisted of salt restriction, mercurial diuretics, and digitalization. She responded fairly well, although a roentgenogram of the chest during the immediate postoperative period showed considerable cardiomegaly. She was finally discharged on Oct. 6, 1954, one month following surgery.



A. *B.* *C.*

Fig. 4.—Case 2. C. C., 8-year-old girl. Shows progressive postoperative cardiac enlargement and marked increase of pulmonary vascular markings. *A*, Before infundibulectomy. *B*, Two months after infundibulectomy. *C*, Nine months after infundibulectomy.

She did well until November 12, when she was noted to have some swelling of her feet and ankles. She was seen for follow-up examination Nov. 17, 1954. At this time there was no evidence of peripheral cyanosis. The liver edge was just palpable. There was no edema. The heart rate was 96 per minute and regular. A Grade 5, coarse, harsh, prolonged systolic murmur with a Grade 2 systolic thrill was noted at the left border of the sternum in the second intercostal space. A Grade 2, decrescendo diastolic murmur was also heard over this area. Fluoroscopic study and roentgenogram (Fig. 4) showed the heart to be at the upper limits of normal in size. The lungs were clear peripherally. The hilar vascular markings were increased. There was enlargement of both ventricles. A right bundle branch block was noted on the electrocardiogram. Right ventricular hypertrophy persisted, but there was also a first degree atrioventricular block. She was continued on salt restriction and diuretics.

When seen on Jan. 26, 1955, she seemed to tire more easily and occasionally would have some vomiting and coughing of mucoid material. She was tachypneic with a respiratory rate of 44 per minute. The auscultatory findings showed no change except for the diastolic murmur which was

now Grade 3. Fluoroscopic study showed increased pulsatility in the hilar vessels. A roentgenogram showed further cardiac enlargement. During the next 3 months she continued to have intermittent decompensation of both ventricles and was readmitted on April 24, 1955. At this time the findings were essentially as before. Right heart catheterization (Table I) was repeated June 16, 1955, with the following changes: (1) an increase of the arterial oxygen saturation in the femoral artery, (2) practical abolition of the pulmonary stenosis as indicated by 8 mm. Hg systolic pressure gradient between the right ventricle and the pulmonary artery, (3) a marked degree of pulmonary regurgitation, as demonstrated by no gradient of the diastolic pressure between the right ventricle and the pulmonary artery, (4) a marked elevation of the diastolic pressure in the right ventricle indicating a severe degree of right ventricular failure, (5) marked elevation of the pressure in both the right atrium and the pulmonary artery wedge area, indicating right and left ventricular failure, and (6) an increase of PF/SF ratio indicating an increase of pulmonary blood flow. The hemoglobin had now decreased to 16.2 Gm. per cent. It was believed that she now had a marked left-to-right shunt and increased pulmonary blood flow with pulmonary regurgitation and intermittent failure of both ventricles. She was sent home on essentially the same medical regimen.

In June, 1955, she complained of coughing and sneezing at night and upon examination by her physician was noted to be decompensated. Rehospitalization was carried out and mercurial diuretics were given. The electrocardiogram and roentgenogram are shown in Figs. 3 and 4, respectively. During the next 2½ months she had congestive heart failure intermittently, and on Oct. 3, 1955, became rather lethargic, drowsy, and oliguric. Examination showed generalized anasarca. Death came suddenly at home, and permission for autopsy was not obtained.

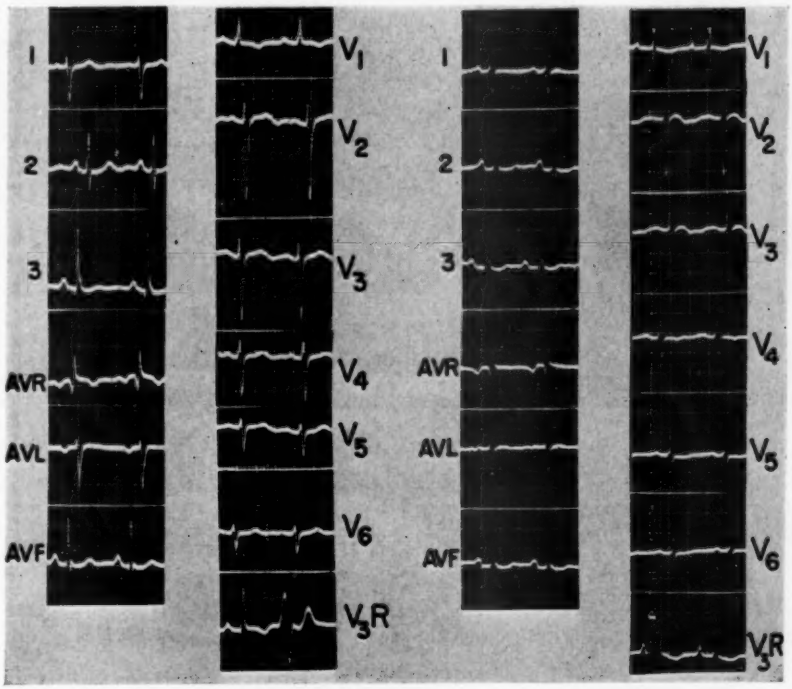
Comment: This is a case of Fallot's tetralogy with infundibular stenosis. After infundibular resection, progressive cardiac enlargement developed, right bundle branch block became manifest, the dominant shunt was left to right, severe pulmonary hypertension was present with practically complete abolition of the pulmonary stenosis, and severe pulmonary valvular regurgitation developed. Death occurred with cardiac decompensation and congestion of both circulations.

CASE 3.—D. T., a 19-year-old boy, was first seen at the University of Kansas Medical Center in November, 1955. Information was obtained from him and his parents indicating that he had been cyanotic with exercise since the age of 2 years, and that this had become progressively worse. Minimal exercise produced dyspnea, increase in the cyanosis, fatigue, and occasionally some squatting. He was mentally retarded, having been passed in school only because of his age. The past history was otherwise noncontributory.

Physical examination showed a dull-appearing, thin, short boy, 19 years old, whose height was 63 inches and weight 100 pounds. His blood pressure was 110/75 mm. Hg in both arms. The peripheral pulses were normal. He was very definitely cyanotic, this being particularly evident in the mucous membranes of the mouth and conjunctivae. The heart was questionably enlarged to the left, but no definite thrills were felt. Upon auscultation, the second sound over the pulmonary area was noted to be louder than that in the aortic area, but not accentuated. There was a Grade 3, somewhat prolonged systolic murmur heard over the entire precordium, but loudest at the left sternal border in the second and third intercostal spaces. The lungs were clear and the liver and spleen were not enlarged. There was moderate clubbing of the fingers.

The electrocardiogram showed right ventricular hypertrophy (Fig. 5). The hemoglobin was 20.0 Gm. per cent and hematocrit 58 per cent. A roentgenogram of the chest (Fig. 6) confirmed the fluoroscopic impression of slight cardiac enlargement, primarily right ventricular. The hilar vascular markings were essentially normal. However, the main pulmonary artery was slightly prominent. There was reduced vascularity in the peripheral fields of the lung. The impression at this time was tetralogy of Fallot, and he was admitted to the hospital in February, 1956, for catheterization of the right heart (Table I), which demonstrated the following findings: (1) a localized pulmonary infundibular or valvular stenosis as noted by a sudden systolic pressure grad-

ient between the right ventricle and the main pulmonary artery, (2) evidence of a "common functioning ventricle" as indicated by essentially identical systolic pressures in the right ventricle and the femoral artery, and (3) a right-to-left shunt as indicated by oxygen desaturation of the femoral artery. Psychometric testings were obtained showing an I. Q. of 64. It was decided to carry out a pulmonary valvotomy in an effort to increase his tolerance for exercise. This was done Feb. 15, 1956, by the transventricular route, utilizing an infundibular punch as well as the Brock knife. Small bits of tissue were removed from the pulmonary valve both anteriorly and posteriorly. Immediately prior to the procedure the right ventricular systolic pressure was 120 mm. Hg; following the operative intervention it fell to 80 mm. Hg. The pulmonary artery pressure rose slightly.



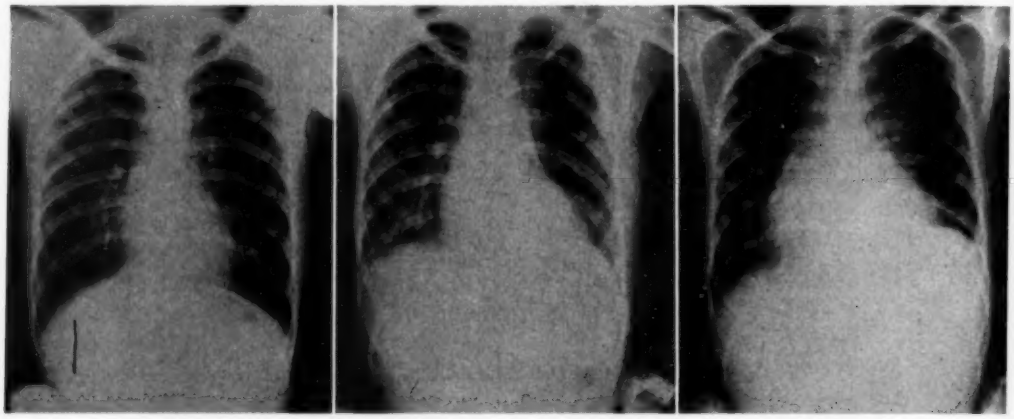
A. *B.*

Fig. 5.—Case 3. Shows the increased amplitude of R wave at V_6 after operation. *A*, Before operation (11-30-55). *B*, Fifty-four days after partial pulmonary valvectomy (4-8-56).

The postoperative course was relatively uneventful. He did seem to be considerably improved symptomatically and the oxygen saturation of the femoral artery was 91.4 per cent. The hemoglobin gradually fell to 13.2 Gm. per cent. Re-fluoroscopy showed increase in the amount of pulmonary blood flow. The cardiac size was increased as observed by roentgenogram (Fig. 6). A Grade 2, decrescendo diastolic blow was now noted over the pulmonic area. He was discharged home on the fourteenth day postoperatively.

He was seen one month later (March 30, 1956) and was symptomatically better. He had increased tolerance for exercise, being able to walk a half mile. He was sleeping flat in bed and had no squatting or cyanosis. The physical examination showed no visible cyanosis and the clubbing of the fingers was diminishing. He looked quite well. The pulse rate was 110-115 per minute at rest. The auscultatory findings were those of a Grade 4+, harsh systolic murmur with a Grade 3 systolic thrill noted at the left sternal border in the third intercostal space. This was followed by a Grade 3, decrescendo diastolic blow. The liver was not enlarged and the lungs were clear. There was no peripheral edema. Fluoroscopic study of the heart, confirmed by a roentgenogram (Fig. 6), showed the heart to be considerably increased in its transverse diameter. The lung fields were quite congested with increased pulmonary blood flow, and the right ventricle was now

markedly enlarged. The pulmonary vessels near the hilar region pulsated rather vigorously. It was advised that he be readmitted to the hospital for further evaluation. Upon hospitalization, shortness of breath and then episodes of nocturnal dyspnea were evident. The resting heart rate was 110. A diastolic gallop rhythm was distinctly present. There was slight venous engorgement over the neck. No râles nor fluid could be demonstrated in the chest. The liver and spleen were not palpable. The venous pressure was 190 mm. of normal saline. The circulation times were: arm to lung (ether) 20 seconds and arm to tongue 35 seconds (Decholin). The patient was digitalized, with improvement of his symptoms. His resting heart rate also slowed to 80 per minute. Right heart re-catheterization was done with the following findings: (1) an increase of the



A. *B.* *C.*

Fig. 6.—Case 3. D. T., 19-year-old male. Shows progressive postoperative cardiac enlargement and marked increase of pulmonary vascular markings. *A*, Before partial pulmonary valvectomy. *B*, Four days after partial pulmonary valvectomy. *C*, Forty-eight days after partial pulmonary valvectomy.

oxygen saturation in the femoral artery, (2) a rise of the pressure in the pulmonary artery, (3) an elevation of the mean pressures in both the right atrium and the pulmonary artery wedge area indicating failure of the "common ventricle," and (4) an increase of pulmonary blood flow as indicated by a left-to-right shunt and an increase of PF/SF ratio. The elevation of the pulmonary artery wedge pressure (19 mm. Hg?) higher than that of the pulmonary diastolic pressure may be explained either by the posterior location of the tip of the cardiac catheter or an unreliable reading. He was discharged home on a low-salt diet and maintenance digitoxin.

The follow-up examination on May 11, 1956, demonstrated the same findings, except for a triple rhythm present at the apex. However, his physician reported that in the last 3 months of life he developed a downhill course of biventricular failure manifested by pulmonary congestion, marked hepatosplenomegaly, and anasarca. He died of intractable heart failure on Aug. 9, 1957. Autopsy was not obtained.

Comment: This is a case of Fallot's tetralogy with pulmonary valvular stenosis. Postoperatively the patient developed cardiac enlargement, moderate left-to-right shunt at the ventricular level, pulmonary valvular regurgitation, and cardiac decompensation. Compensation was being maintained by the usual methods. Following a transient improvement, he succumbed to decompensation of both circulations.

DISCUSSION

Shortly after surgery these 3 patients showed improvement, with remarkable changes consisting of disappearance of cyanosis, increase of exercise tolerance,

and a feeling of well being. This was in contrast to the other 22 patients in this study with a Brock procedure who showed slower improvement, but better long-term results. However, two of our three cases developed symptoms and signs of biventricular failure. Dyspnea, orthopnea, and nocturnal dyspnea indicated left ventricular failure, while hepatomegaly and peripheral edema indicated right ventricular failure. One case showed marked cardiac enlargement, but with improvement of tolerance for exercise.

Cardiac Physical Findings.—The postoperative cardiac physical findings were rather striking, as compared with the preoperative evaluation. These changes are summarized in Table II. Increases in the intensity of the pulmonary second sound were observed. The intensity of the pulmonary systolic murmur increased and usually was associated with the development of a pulmonary systolic thrill probably due to increased pulmonary flow. The postoperative appearance of a pulmonary diastolic murmur probably represents pulmonary regurgitation. The signs of pulmonary edema and systemic venous congestion depended on the degree of congestive failure.

TABLE II. PERTINENT PHYSICAL FINDINGS BEFORE AND AFTER OPERATION

PATIENT	INTENSITY OF SECOND SOUND OVER PULMONARY AREA*		PULMONARY MURMUR†				PULMONARY THRILL‡ (SYSTOLIC)	
			SYSTOLIC (GRADE)		DIASTOLIC (GRADE)			
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
L.S. (Case 1)	N	N	2	4	0	2–3	0	1–2
C.C. (Case 2)	1	2	3	5	0	2	0	2
D.T. (Case 3)	N	1	3	4–5	0	3	0	3

N = Normal.
*Abnormal accentuation of second sound.
†Murmurs graded 1 to 6.
‡Thrill graded 1 to 4.

Fluoroscopy and Roentgenogram Findings.—Serial fluoroscopies and roentgenograms of the chests also revealed progressive changes, mainly biventricular enlargement, active forceful systolic pulsations of both ventricles, increased pulmonary vascular markings, and excessive pulsatility of the pulmonary arteries.

Electrocardiographic Changes.—Two of the three cases developed postoperative right bundle branch block[7] (Cases 1 and 2). There was increased left ventricular muscular mass as noted by the greater amplitude of the R wave in Lead V_6; this was due probably to the onset of the large left-to-right shunt through the ventricular septal defect as in Cases 1 and 3.

Cardiac Catheterization Studies.—Table I summarizes the cardiac catheterization studies. Figs. 7, 8, and 9 show the pre- and postoperative pulmonary artery and right ventricular pressure curves. Fig. 10 shows the preoperative and postoperative changes in the right atrial pressure. These may be commented upon with regard to three aspects:

1. Pressure patterns: Tracings of caval and right atrial pressures showed an increase of their mean pressure and amplitude of the wave (Fig. 10). These changes may be explained on the basis of ventricular failure. There was no change in the right ventricular systolic pressure. The increase of pulmonary systolic and reduction of pulmonary diastolic pressure constituted a pattern of pulmonary regurgitation. There were striking rises of the pulmonary artery wedge pressure and mean right atrial pressure, probably secondary to the failing "common ventricle."

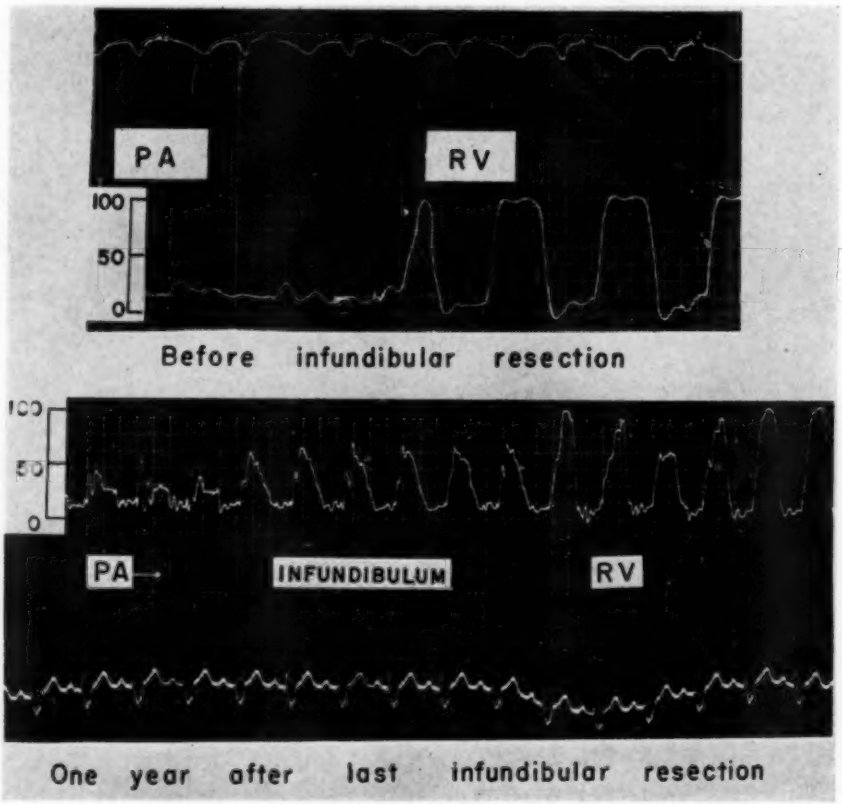


Fig. 7.—L. S., male, 22 years old. Upper tracing shows systolic pressure gradient between the main pulmonary artery and the right ventricle. Lower tracing shows combination of pulmonary valvular and infundibular stenosis with pulmonary valvular regurgitation.

2. The peripheral oxygen saturation uniformly increased. There was a subsequent fall of hemoglobin and hematocrit. The postoperative rise in oxygen saturation in the femoral artery was explained by the lowered pulmonary outflow resistance and a subsequent decrease in the flow from right to left through the ventricular septal defect.

3. Calculations of blood flow showed the development of a large left-to-right shunt through the ventricular septal defect concomitant with the fall in the right-to-left shunt. This further demonstrated that the major factors con-

trolling the direction of the shunt were the relative pulmonary and systemic resistances and size of the ventricular defect, rather than the overriding aorta.[8-11] The change of the pulmonary resistance is clearly indicated in Table III. The resultant right bundle branch block may further aggravate the left-to-right shunt because of the delayed right ventricular contraction.

The right and left atrial pressure levels are greatly influenced by an adequate amount of venous filling, atrioventricular resistance, and ventricular condition. In the absence of tricuspid or mitral stenosis the ventricular status becomes a major factor in Fallot's tetralogy. The venous filling pressure usually is affected secondarily by the ventricular decompensation. The abnormal elevation of the atrial pressure may be due to the following conditions: (1) an increase of atrioventricular resistance due to a lesser distensibility of a hypertrophied ventricle,

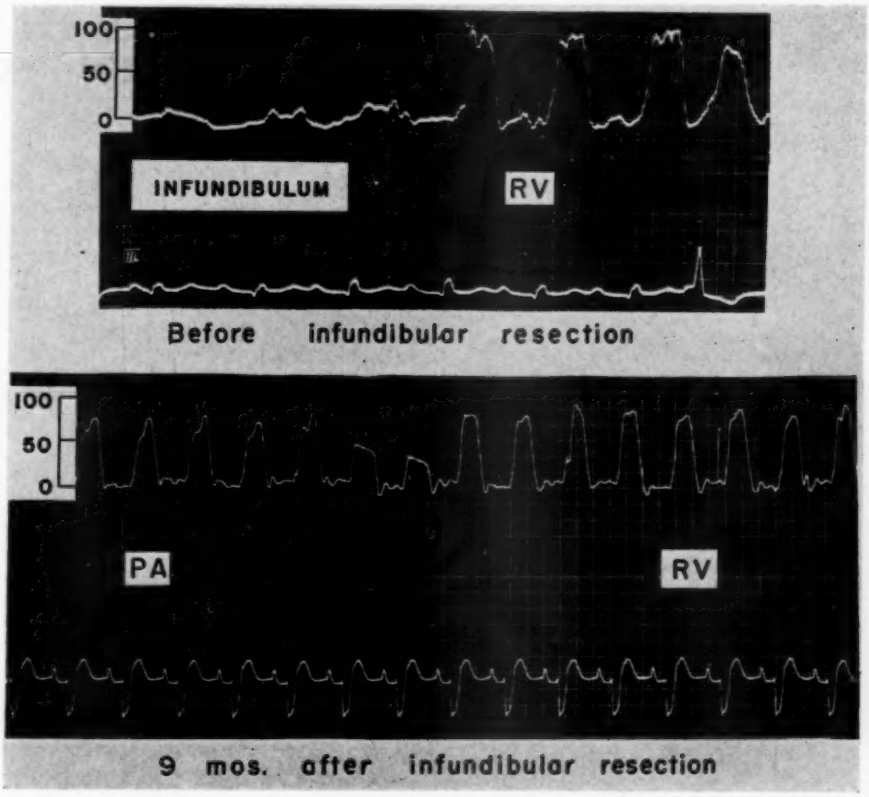


Fig. 8.—C. C., 8-year-old girl. Upper tracing demonstrates pulmonary infundibular stenosis. Lower tracing shows a marked pulmonary valvular regurgitation after infundibular resection.

(2) a functional tricuspid or mitral insufficiency, and (3) an increase of the ventricular diastolic pressure in the failing ventricle. In our cases the latter factor is probably the main cause producing congestion in both systemic and pulmonary circulations. The ventricular work is roughly calculated by the mean aortic or pulmonary systolic ejection pressure multiplied by the ventricular output. However, the exact amount of ventricular diastolic shunt which does not require any

TABLE III

NAME SEX AGE (YR.)	DATE	O_2 CONS. (C.C./MIN.)	PRESSURE S./D. (MEAN)		O_2 CONTENT (VOL. %)		O_2 CAPACITY (VOL. %)	BLOOD FLOW (C.C./MIN.)		PF/SF RATIO	RESISTANCE (DYNES-SEC.-CM.$^{-5}$)	
			PA	FA	PA	FA		PF	SF		TPR	TS
D.T. Male 19	Preop. 2/9/56	188	17/7 (10)	120/80 (68)	20.9	24.2	28.4	3082	5696	0.54	259	1325
	Postop. 4/9/56	161	52/8 (34)	120/80 (68)	16.9	21.6	22.8	3500	2260	1.54	776	2404

PA = pulmonary artery; FA = femoral artery; PF = pulmonary flow; SF = systemic flow; O_2 cons. = oxygen consumption; TPR = Total pulmonary resistance; TS = Total systemic resistance; S./D. = Systolic /diastolic.

ventricular work cannot be measured. Therefore, the right or left ventricular work cannot be calculated. Since the systolic pressures in both ventricles and the diastolic pressures (RA and PAW) are identical (Table I) in both preoperative and postoperative studies, it is probably justifiable to say that the two ventricles function as a "common chamber." This is clearly indicated in Cases 2 and 3. The pulmonary resistance normally is much lower than that of the systemic circulation. Once the obstruction of the right ventricular outflow tract is relieved by surgical means, the pulmonary blood flow is considerably increased. The overdistended and overloaded left atrium after surgery may deliver a rapid left ventricular filling which may give a considerable left-to-right ventricular diastolic shunt. The sudden reversal of ventricular shunt and the development of a varying degree of pulmonary regurgitation seemingly are the underlying causes producing a failure of this "common chamber." It has been demonstrated that the pulmonary artery wedge pressure is a reflection of the left atrial pressure.[12-14]

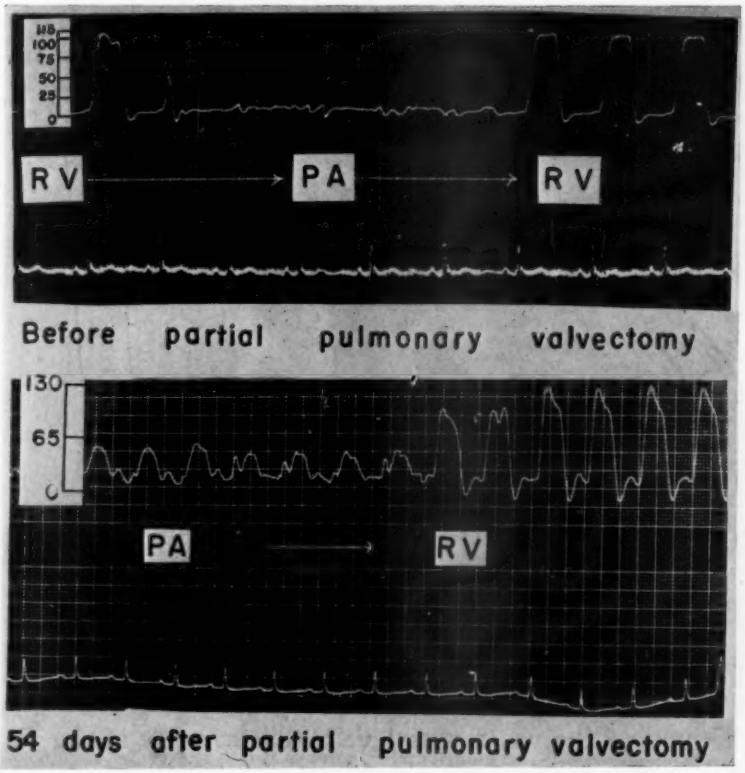


Fig. 9.—D. T., 19-year-old male. Upper tracing shows marked pulmonary valvular stenosis. Lower tracing shows mild pulmonary valvular stenosis, pulmonary regurgitation, and mild pulmonary hypertension.

Therefore, the identical elevation of the pressures in the right atrium and pulmonary artery wedge area is supported by the evidence of congestion in both circulations. Without taking a roentgenogram of the chest in the lateral position to determine the anterior or posterior location of the tip of the cardiac catheter, the value of the pulmonary artery wedge pressure cannot be measured accurately.

The natural life history of this group of patients with a ventricular septal defect, identical pressure readings in both ventricles, a certain degree of pulmonary stenosis, a dominant left-to-right ventricular shunt, and pulmonary hypertension with pulmonary regurgitation, has not been studied. In some respects these cases are similar to those with pulmonary stenosis and left-to-right

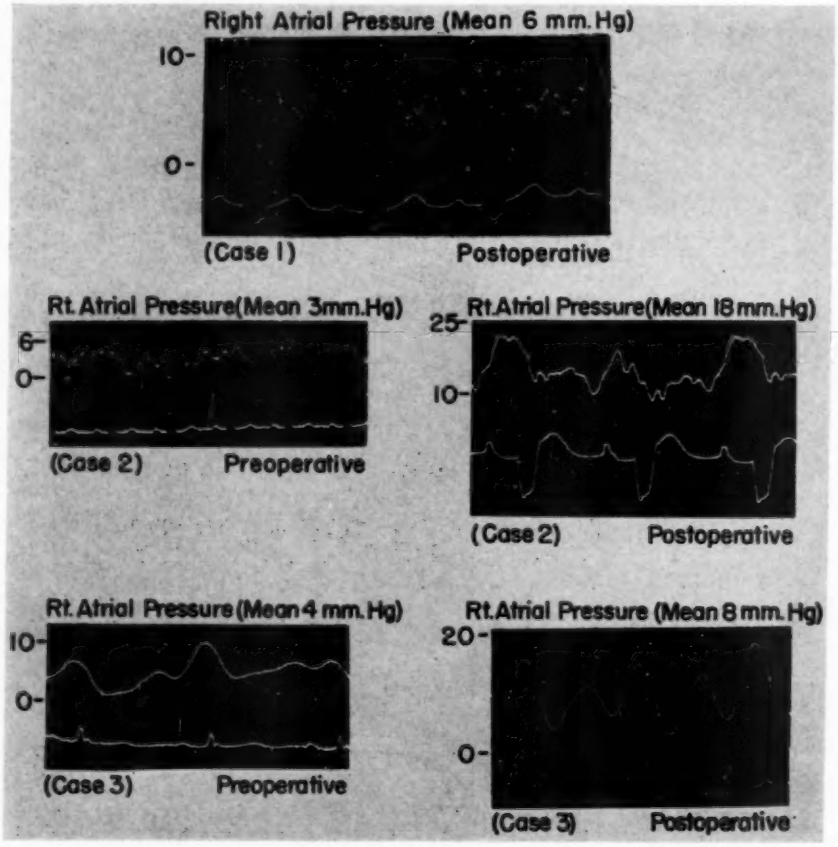


Fig. 10.—Preoperative and postoperative changes in right atrial pressures.

ventricular shunt and also to so-called "Eisenmenger's syndrome." Do these patients eventually develop pulmonary arteriolar sclerosis? Do they re-develop right-to-left shunt at the ventricular level? The severity of the pulmonary hypertension, the amount of left-to-right shunt, and the myocardial reserve are the determining factors in the prognosis.

SUMMARY AND CONCLUSIONS

Three cases of Fallot's tetralogy which were operated either by pulmonary valvectomy or by infundibular resection are presented. Cardiac decompensation of the "single functioning ventricle" led to death in two instances. The pre- and postoperative hemodynamic data are presented and discussed. Because of the

potentially serious cardiophysiodynamic changes which may occur postoperatively, and since the operative procedure does not correct the ventricular septal defect, this surgical approach to Fallot's tetralogy should be considered only as palliative and not without hazard.

We wish to thank Herbertine Clark, Margie Delich, Joanne Clifford, Margie Allen, and Eleanor Lane for their technical assistance in making this publication possible.

REFERENCES

1. Blalock, A., and Taussig, H.: J.A.M.A. **138**:189, 1945.
2. Potts, W. J., Smith, S., and Gibson, S.: J.A.M.A. **132**:627, 1946.
3. Brock, R. C., and Campbell, M.: Brit. Heart J. **12**:403, 1950.
4. Brock, R. C.: Am. J. Med. **12**:706, 1952.
5. Campbell, M., Deuchar, D. C., and Brock, R. C.: Brit. M. J. **2**:111, 1954.
6. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:523, 1924.
7. Kittle, C. F., Santos, E. M., and Dimond, E. G.: Am. Surgeon **22**:80, 1956.
8. Eisenmenger, V.: Wien. klin. Wchnschr. **11**:25, 1898.
9. Edwards, J. E., Dry, T. J., Parker, R. L., Burchell, H. B., Wood, E. H., and Bulbulian, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels, Springfield, Ill., 1954, Charles C Thomas.
10. McCord, M. C., and Blount, S. G., Jr.: Circulation **11**:754, 1955.
11. Callahan, J., Brandenburg, R. O., and Swan, H. J. C.: Circulation **12**:994, 1955.
12. Hellems, H. K., Haynes, F. W., Dexter, L., and Kinney, T. D.: Am. J. Physiol. **155**:98, 1948.
13. Dow, J. W., Dexter, L., Haynes, F. W., Wittenberger, J. L.: J. Clin. Invest. **28**:778, 1949.
14. Lagerlöf, H., and Werkö, L.: Scandinav. J. Clin. & Lab. Invest. **1**:147, 1949.

Review

The Structure of the Renal Glomerulus

C. Barber Mueller, M.D., Syracuse, N.Y.

The renal corpuscles have been the subject of considerable anatomic and functional interest since their discovery by the great anatomist, Malpighi.[82] They are a striking example of the unity of structural and functional knowledge, for, from the days of their discovery, increasing knowledge of their structure has been paralleled by changing concepts of their function. This review is an attempt to highlight the anatomic contributions made by a multitude of investigators and to present in survey the development of concepts of the various structures found in the glomerulus. Since it is impossible to refer to every author's concept of each of the many facets of structure, I have tried to present the salient ideas, the major contributions and the points of difference between various workers.

Malpighi discovered the glomerulus by injection of the renal artery, and he considered it to be a gland which gave rise to the uriniferous tube. Schumlansky,[110] in 1782, very clearly described the intimate arrangement between glomerulus and tubule and denied the generally held concept that the glomerular tuft emptied directly into the tubule. The classic studies of Bowman,[15] in 1842, on the structure of the glomerulus are quite remarkable when viewed in the light of 115 subsequent years of fairly continuous structural investigation. Bowman[15] was particularly interested in the structure and course of the renal arteries and their relationship to the glomerulus. His investigations were made by injecting solutions of potassium dichromate and lead acetate into the renal artery. This gave him the "clearest evidence that the capsule which invests them [the Malpighian corpuscles] is, in truth, the basement membrane of the uriniferous tube expanded over the tuft of vessels." He noted that all of the blood of the renal artery passed through the tuft and then into a capillary plexus which surrounded the tubule, before leaving the kidney via the renal vein. He described the course of the afferent vessel into the glomerulus where it "perforates the capsule, and, dilating, suddenly breaks up into two, three, four, or even eight branches, which diverge in all directions like petals from the stalk of a flower, and usually run, in a more or less tortuous manner, subdividing again once or twice as they advance,

From the Department of Surgery, State University of New York Upstate Medical Center, Syracuse, N. Y.

Supported by U. S. Public Health Service Grant No. A-1393 (C), National Institutes of Health, Bethesda, Md.

Received for publication Oct. 11, 1957.

over the surface of the ball they are about to form. The vessels resulting from these subdivisions are capillary in size, and consist of a simple, homogeneous, and transparent membrane. They dip into its interior at different points, and after further twisting, reunite into a single vessel, which varies in its size, being generally smaller, but in some situations larger than the terminal twig of the artery. This vessel emerges between two of the primary divisions of the terminal twig of the artery, perforating the capsule close to that vessel, and, like it, adhering to this membrane as it passes through. It then enters the capillary plexus which surrounds the tortuous uriniferous tubes." He declared that "The whole circumference of every vessel composing the tuft is also free, and lies loose in the cavity of the capsule. These circumstances cannot be seen in specimens gorged with injection, but only by careful examination of recent specimens with a power of 200 or 300 diameters. The vessels are so perfectly bare, that in no other situation in the body do the capillaries admit of being so satisfactorily studied. It is only where the tuft is large, as in Man and in the Horse, that its lobulated character can be always discerned." He was explicit in his description of the basement membrane which now bears his name, and stated that it is a "simple homogeneous, and perfectly transparent membrane, in which no structure can be discovered. It is perforated, as before stated, by the afferent and efferent vessels, and is certainly not reflected over them. They are united to it at their point of transit, but in what precise manner I have not been able to determine." He described the difference in the shape, size, and course of the efferent vessels as they are related to the cortical and juxtamedullary area. He defined and described the two capillary systems of the kidney and proposed that the vessels which carry blood between these two capillary systems be termed a portal system. He speculated upon the function of the Malpighian corpuscle to the effect that it was "an apparatus destined to separate from the blood a watery portion," and, "now, however, that it is proved that each one is situated at the remotest extremity of a tube, that the tufts of vessels are a distinct system of capillaries inserted into the interior of the tube, surrounded by a capsule, formed by its membrane and closed everywhere except at the orifice of the tube, it is evident that conjectures on their use may be framed with greater plausibility." Bowman's concept that the vessels were bare, and his statement that the vessels lie coiled freely within the space of his capsule have been shown to be untrue.

THE ARRANGEMENT OF THE CAPILLARIES IN THE TUFT

Within the media of the afferent artery a change in the nature and appearance of the muscle cells has been observed and described by many investigators—Goormaghtigh[39,41,43] called this segment the *juxta-glomerular neuro-myo arterial* segment, and Zimmerman[127,128] named these cells *cushion* or *polkissen* cells. Their function, if any, has remained a mystery. Goormaghtigh felt that these cells, a transition from the muscular coat of the afferent artery, extended into the glomerular tuft and comprised a stalk around which the glomerular capillary spiraled. At one time he thought that the intraglomerular portion—the stalk—might even act in its neuromuscular capacity to regulate blood flow through the glomerulus.[40] Ruyter,[108] studying these cells in the mouse, noted that the muscle

cells of the tunica media were composed of granular cells and that the internal elastic lining lost some of its staining properties. Such changes were seen to extend for variable distances along the wall of the artery and appeared during the first week of postnatal life. Hartroft[55,56] recently demonstrated changes in these cells associated with alterations in adrenal cortical activity and sodium metabolism.

Once within Bowman's capsule, the artery divides into several branches, each branch giving rise to one lobe or lobule. Bowman described these vessels as dividing repeatedly, then reuniting to form the sinus of the efferent artery. Borst,[14] in describing the glomerulus, noted that the afferent vessel formed a large lake at the entrance of the glomerulus, and stated that from two to five trunks came from it. Johnston,[59] in 1900, made wax reconstuctions of a glomerulus from serial sections. He found that the afferent artery divided immediately into five branches and that the efferent vessel is reconstituted within the tuft at the level of the equatorial plane. He felt that, in addition to many connections between the capillaries of one lobule, several lobules were connected to each other. He described several lengths of the paths through the tuft, the shorter one being smaller in diameter and more tortuous than the longer. "Lobulation when it appears at all is superficial." "In addition to the many connections between capillaries of the same group, the three groups or lobules are intimately connected with one another with numerous anastomoses." "The number and varied character of these connections show the impossibility of dividing the capillaries of the glomerulus completely into distinct groups." Injection studies of the glomerular vessels have been reported by Vimtrup,[119] Wilmer,[122] and Hall.[52] Vimtrup, in 1928, concluded that the vessels are "long slender vessels, more or less coiled, which never present anastomoses. There was never any trace of the injection mass in the vas efferens unless at least one complete capillary loop was injected." He did not find "short-cut anastomoses." Wilmer, in 1941, using celloidin injections and maceration in acid, was unable to see any anastomoses between capillaries. Hall, who in 1954 studied a series of latex injections of the glomerular tuft capillaries, feels that each of the two to eight lobules arises by division of the afferent arteriole. Each lobule is comprised of a relatively large central vessel which courses into the capsular space, divides several times, and receives the separated branches prior to its egress as the efferent arteriole. He saw many fine anastomoses which, in a lateral fashion, join the various channels in any one lobule, but do not extend between lobules. His description confirms that made some 80 years ago by Ludwig,[67] who stated that the glomerulus was composed of several vascular lobules, continuous at either end with an artery and a vein.

In 1952, Trabucco and Marquez[115] reported a study of the glomerulus made by India ink and latex injections. They concluded that the glomerular bundle actually consists of saccular outpouchings of a single vessel. They denied the generally held concept that blood coursed from afferent to efferent vessel via a capillary system in the tuft. Few workers now consider their concept of glomerular structure plausible.

Allen,[4] in 1926, made reconstructions of the gross characteristics of the lobule

in a case of chronic diffuse glomerulonephritis. He concluded that the interlobular spaces penetrated to the deeper parts of the glomerular tuft, that the lobules were confluent at the hilus, and that no uniformity of lobular configuration was apparent.

Boyer,[16,17] in 1956, studied the pattern of the glomerular capillary lumens by making India ink injections, serial sections, wax reconstruction of camera lucida drawings, and then a plastic mold of the capillary spaces. He described the tuft as a true rete with many anastomoses extending between the various vessels and from one lobule to another. He recognized the lobular nature of the tuft when seen in sagittal section through the hilus but claimed that interlobular connections were frequent, confirming Johnston's observations of 50 years ago.

THE BASEMENT MEMBRANE OF BOWMAN'S CAPSULE

The expanded upper end of the proximal convoluted tubule, Bowman's capsule, has long been recognized as having two distinct portions—the basement membrane and an overlying layer of epithelium. Each of these structures is continuous with its counterpart in the proximal convoluted tubule.[20] The basement membrane of Bowman's capsule has been described as having two layers—an outer reticular zone and an inner, clear, homogeneous zone.[22,23,38,68,78,79,80,85,106,107,120] In this review, the term *capsular basement membrane* will be used to describe the homogeneous portion of that membrane, since the reticulum fibrils embedded in its external surface appear to be a part of the over-all supporting structure of the kidney, and not an inherent part of either this membrane or its continuation as the basement membrane of the tubule.

Mall,[79,80] in 1891, made an intensive study of the staining properties of the two parts of the basement membrane of Bowman's capsule before and after digestion with pancreatin. He concluded that reticulum fibrils comprise an outer zone but that they do not form the capsular basement membrane, which could be digested by pancreatin. He described a complex, anastomosing, interlacing network of reticulum fibrils extending from the renal capsule to the renal pelvis, within which are supported the multitude of vessels and nephron units. Rühle[106] and Russakoff[107] demonstrated homogeneous and reticulated layers of the basement membrane of Bowman's capsule and felt that both layers were produced by peritubular capillary endothelial cells. Corner[22] studied the embryology of the glomerular and tubular basement membranes and concluded that the capillary endothelial cells generally produced the reticulum fibrils of the kidney except when the endothelium was intraglomerular. He wrote, "In the renal cortex, between the convoluted tubules and about the glomerolus, the 'stroma' is no more or less than a network of reticular fibrils embedded in the cytoplasm of the capillary endothelium or deposited by the latter against the tubules and Bowman's capsule. True fibroblasts are very infrequent—perhaps altogether absent." "The endothelium of the glomerular tuft is in no case provided with reticulum, affording a marked contrast to that of the intertubular capillaries." "It seems, therefore, that capillary endothelium can form reticulum fibrils in those organs whose blood capillaries come into direct contact with active secreting epithelial cells. Where support of tissues is by connective tissue the endothelium seems

devoid of reticulum fibrils." Corner's conclusions were based upon the observation that with Mallory's stain the glomerular basement membrane decolorizes more rapidly than the tubular basement membrane, and that under abnormal conditions of disease fibrous tissue is produced more readily in the intertubular reticulum than in the glomerulus.

THE BASEMENT MEMBRANE OF THE GLOMERULUS

The glomerular basement membrane completely encloses the glomerular endothelial mass and the capillary lumens. Its structure, its origin, and its attachments have been, and remain, points of controversy. It has staining properties which are different from those of the capsular basement membrane and it probably does not contain reticulum fibrils except when immediately adjacent to the hilus. Bowman claimed that the vessels of the tuft perforated the capsule, which was "certainly not reflected over the vessels." MacCallum[78] stated that the basement membrane of Bowman's capsule, which is continuous with that of the tubule, is seen to turn back upon itself and surround the capillaries of the tuft. He claimed that the basement membrane, after covering the outer surface of a capillary, continued across a space to cover the outer surface of the next capillary, with but little depression between them. McGregor,[68] Bohle,[13] and Elias[29] felt that a basement membrane from the afferent and efferent vessels joined with the basement membrane of Bowman's capsule to form jointly the glomerular basement membrane. Hall,[49,52] on the other hand, feels that the basement membrane of Bowman's capsule is pierced by the vascular tuft whose basement membrane is a continuation of that which surrounds the hilar vessels and is not continuous with that of the capsule and the tubules. Mueller[87] has electron microscope pictures apparently demonstrating the continuity of the capsular basement membrane with the glomerular basement membrane, and feels that these two membranes are really one continuous structure. Mall,[80] in 1901, felt that he had demonstrated that the capsular membrane turns in to cover the tuft, but that the reticulum enters only a short way with the vessels.

Most basement membranes in the body stain like reticulin with appropriate silver staining techniques, but the glomerular basement membrane is negative to silver impregnation and the normal glomerulus contains a meager amount of argyrophile fibers.[11] Gersh and Catchpole[38] felt that reticulin staining properties were due to collagen fibrils set in a glycoprotein matrix, and they demonstrated that the glomerular basement membrane was, in the greatest extent, devoid of such fibrils. As yet such fibrils have not been found by electron microscopy of the glomerulus.[6,12,28,29,35,49,52,86,88,91,97,98,101,102,105,109,114,124]

At the magnifications possible by electron microscopy, the capsular basement membrane can be seen to be a laminated, dense material of a fibrillar nature with a multitude of fuzzy reticulum fibrils on the external surface, in keeping with descriptions of the older anatomists.[86] The glomerular basement membrane, on the other hand, is of a homogeneous nature and, to date, no one has reported the glomerular basement membrane to be fibrillar.

Considerations raised by a knowledge of the embryology of the glomerulus[2,22,57] and by staining properties of the diseased glomerulus[8,11,60-62,73,74] led the

light microscopists to a concept that the apparently single basement membrane of the normal glomerulus was in reality composed of two basement membranes—one continuous with the basement membrane of Bowman's capsule (the subepithelial membrane) and the other continuous with the basement membrane of the arterioles (the capillary membrane). These were thought to be indistinguishable in the normal glomerulus because of their proximity to each other, but were felt to be identifiable when separated by disease.[60,62] Zimmerman[128] stated that he was able to distinguish two basement membranes—the first, a subepithelial membrane, and the second, an extremely thin capillary basement membrane. He held that these two, together with a thin optically-inseparable endothelium, form the capillary wall. He claimed that the subepithelial basement membrane never covers the capillaries (i.e., go entirely around the lumen) but becomes separated from them wherever the capillaries are connected to the intralobular interstitial tissue. At such a point the subepithelial membrane blends with the interstitial tissue and is thickened as it traverses the site of its contact with the interstitial-endothelial cell mass. Allen[1-3] has based his concepts of glomerular disease upon the postulate that two basement membranes exist.

Modern techniques of electron microscopy have established that there is actually but one basement membrane in the normal glomerulus, and all electron microscopic studies of the glomerulus have agreed upon this point. The structure of the basement membrane as seen by the electron microscope is subject, however, to varied interpretation. The earliest micrographs indicated that the capsular surface of the glomerular basement membrane had a serrated or jagged surface[89,102] but failed to demonstrate that these ridges were actually portions of the epithelium. It was postulated that the ridged effect gave strength to the membrane. With the finer techniques now available, it is certain that the membrane is not ridged. Its edges are smooth and parallel, and it usually appears as a homogeneous matrix of varying density when viewed on cross section. Pease,[94] Rhodin,[101] and van Breeman[18] describe the membrane as being the only continuous structure of the wall of the glomerular tuft, since they have described discontinuities in both the endothelial and epithelial layers. Rhodin[101] describes the basement membrane of the rat as having three layers—a central dense layer and two outer, less dense, layers. The central dense layer averages 650 ± 13 Å and the less osmophilic layers on each side are 300 Å thick. The total thickness is thus 1,250 ± 21 Å. Hall[49] states the thickness to be 600 to 800 Å in the rat; Dalton[25] reports 1,600 Å, and Rinehart[105] 800 Å for the rat. Mueller[86] found a thickness of 2,000 to 2,400 Å in man and the dog. Van Breeman and Reger[18] studied the glomerular basement membrane after the feeding of silver nitrate to rats. Tiny deposits of silver could be readily identified in the basement membrane, and by x-ray diffraction studies the deposits were found to be silver sulfide. Sulfhydryl and disulfide groups were identified in the normal glomerular basement membrane by other cytochemical techniques.

The less dense layer of basement membrane adjacent to the epithelial processes led Pease[92] to postulate that the foot processes of the epithelial cells were actually embedded in a cement substance of the basement membrane. Yamada[124] felt that faint membranes extended from the foot processes to the inner layer of

the basement membrane. Such connections as these between epithelial foot processes and the basement membrane have not been described by other microscopists.

Hall[49] believed that in his earliest micrographs he could identify pores in the glomerular basement membrane. He called the membrane the *lamina densa*—a term which included the full thickness of the membrane since he did not identify the three layers subsequently identified by Rhodin and others. His measurements of pore size suggested that the pores were from 50 to 150 Å in diameter, and he postulated that such size was of the proper order to permit the membrane to act as a filter. With refinement of his techniques, however, filtration pores have not been discernible.

THE EPITHELIUM OF BOWMAN'S CAPSULE

The epithelium of the normal Bowman's capsule is a layer of thin, flattened cells that bulge out in the portion that contains the nucleus. The cell borders are distinct,[68] and this layer of cells is continuous with the epithelium of the proximal convoluted tubule. In mice the epithelium of Bowman's capsule is low cuboidal in nature. In disease and under the influence of certain hormones this epithelial layer undergoes marked changes. Testosterone given to mice by Selye[111] caused hypertrophy of these cells—they became larger and assumed the appearance of low columnar or high cuboidal epithelium and, on occasion, even developed brush borders similar to the proximal convoluted tubule cells. Crabtree[23] showed that with increasing age in mice there is an increase in the number of glomeruli with cuboidal capsular epithelium. This increase fails to occur in the castrated males, but can be restored with parenteral testosterone. Electron microscopic examination of these cells shows them to have a few mitochondria scattered throughout the cytoplasm, but no intricate organization of internal structure such as characterizes the cells of the proximal tubule.[86,100,124]

THE EPITHELIUM OF THE GLOMERULUS

Gerlach,[37] in 1848, described some cells which covered the glomerular capillary tuft and called them epithelial cells. Since then they have been studied by most glomerular microscopists and now are recognized to be a very bizarre, trabeculated cell whose shape defied visualization and accurate description by the light microscopists. In the early development of the glomerular tuft these cells arise from the tubular anlage,[57] and in the fetus and newborn mammal they are cuboidal in nature.[2,22,74] Corner[22] concludes that they are epithelial cells and not vascular or adventitial cells, and thus cannot be called pericytes or Rouget cells in the ordinary sense. Ludwig,[67] in 1872, wrote that "A layer of not very well defined cells with spherical nuclei invests the surface of the capillaries and the exact relations are very obscure. This layer is apparently stretched uniformly over each lobule of which the glomerulus is composed and consequently binds the several vessels together; on the other hand, it is not extended from lobule to lobule, but if continuous at all is only so at their roots." McGregor[68] concluded that this epithelial layer, continuous with the epithelium of Bowman's capsule, was not syncytial, but was a flattened layer of continuous and contiguous cells

covering the glomerular basement membrane. Bensley[11] described a protoplasmic network radiating from the epithelial cell bodies in such a way as to form a basket-like structure only partly covering the free surfaces of the capillaries. He felt that this was a syncytium and rejected previous concepts that the capillaries were covered with a continuous epithelium. He also rejected the postulate that glomerular epithelium was a factor in glomerular permeability. He demonstrated the pericytes of the efferent vessel by silver stains,[10] but was unable to see any true pericytes on the capillaries of the glomerular tuft, although they were present on the intraglomerular portion of the efferent vessel after the confluence of the capillary rete.

Clara[21] called these epithelial cells "epicytes," a name which subsequently was used by Kulenkampff.[66] Zimmerman[125-128] first demonstrated, by the use of Golgi-Kopsch stains, that these cells have branching arms which arborize over the free surfaces of the capillaries in the tuft. He originally called them pericytes[126] because he thought that they were contractile elements controlling the local permeability or size of the vessels. He rejected the term pericyte in his later writings and preferred to call these cells simply *Deckzellen* or surface cells. He recognized that this layer is continuous with the epithelium of Bowman's capsule and the proximal tubule, and stated[128] that the *Deckzellen* not only cover the capillaries but are found to overlie the basement membrane at the points where the membrane is adjacent to the intraglomerular interstitial tissue (mesangium). He described some plump, upright cells and some flattened cells, but in all types the bulk of the cytoplasm was in the area of the nucleus, and many arms or trabeculae extended from the central body, branching in "fir-tree" fashion. Kulenkampff,[66] in 1954, utilized Zimmerman's Golgi-Kopsch stain to study some of the reactions of these cells. He noted a normal arrangement similar to that described by Zimmerman. He injected human urine intravenously into cats, hoping to produce an increase in plasma uriniferous products, and one-half hour postinjection he found a decrease in the number of fine trabeculae. In some areas the trabecular processes seemed to spread and flatten out so that they no longer protruded above the capillary wall. They thus formed an epithelial plate rather than the normal arboreal ramifications. This change was not noted following the administration of diuretics. Von Moellendorff[85] called these cells *Hullzellen* or *Deckzellen* and considered them to be a kind of pericyte, although he recognized that these cells replaced the fetal cuboidal epithelium during the first few weeks of postnatal life.

The unusual nature of these cells has been revealed by electron microscopy. They are a fairly large cell with a nucleus situated in the main cytoplasmic mass. In the normal glomerulus this cell mass gives rise to many trabeculae or arms which branch repeatedly and finally terminate in a mass of small foot processes that interdigitate on the capsular surface of the glomerular basement membrane with foot processes from other trabeculae. Each individual process may be 1 to 1.5μ in length, about 2,200 Å in width, and about 6,000 Å in height.[86] The tip of each process is rounded with a small knob-like projection. Between alternate processes there is a space approximately 200 to 300 Å in width, through which

most microscopists feel that filtrate could pass from the basement membrane into the capsular space without traversing any epithelial protoplasmic barrier. In the electron micrographs of most authors there are views in which a trabecula overlies some of the foot processes. Oberling and Gautier[36,88] had several views in which the space between trabeculae and foot processes was narrow and tortuous, and apparently they were so much impressed by its labyrinthine appearance that they described the space as an *appareil lacunaire peri-capillary* or pericapillary sinus and suspected that this may have some function in the regulation of filtration. The foot processes of the epithelial cells are about 100 to 200 Å from contact with the basement membrane.[86] Policard[97] as well as Rinehart[105] and Yamada[121] found tiny vesicles in the foot processes, and thought that such vesicles might possibly play a part in filtration. Policard, like Oberling, was also impressed by the appearance of a pericapillary sinus and postulated that, if the foot processes should change in size, this space or sinus might act as a submicroscopic sponge.

Most observers have commented upon the presence of mitochondria, Golgi bodies, vesicles, and other cytoplasmic inclusions. No special studies of these intracytoplasmic structures have been reported.

The advent of high resolution microscopy has failed to solve the problem of nomenclature. Hall[49] called the epithelial cells *podocytes*, a name which has received moderate acceptance. He defined the long, branching cytoplasmic processes as *trabeculae* and the slender foot processes as *pedicels*. Recent studies by Farquhar,[31-33] Mueller,[87] and Piel[95,96] indicate that in certain pathologic states, particularly the nephroses, the trabeculated nature of this cell disappears and the foot processes are no longer present. The cell then simply lies on the basement membrane as does, for example, the epithelium of the thin loop of Henle on its basement membrane. In such a situation cell boundaries can be seen, and occasionally in some cells rudimentary foot processes are present in one area and absent in another. Since such alterations produce a *podocyte sans pod*, it seems preferable to call the normal cells simply *glomerular epithelium*. *Trabecula* and *foot process* have received fairly wide acceptance and seem to be worthy terms.

The function of the glomerular epithelial cell has been discussed by some authors. It was originally thought to be a supporting cell, possibly one which helped to keep various glomerular basement membranes apart.[51] Farquhar,[33] Rinehart,[103] Policard,[97] and Yamada[124] suggest the possibility that the intracytoplasmic vesicles which are seen indicate an active participation in the filtration process. Recent studies of pathologic material in which the intricate foot process organization is absent and in which the epithelium is everywhere applied to the basement membrane leave little room for doubt that filtration can and does occur through epithelial cytoplasm.[31-34,58,87] Kulenkampff's[66] work suggests that these changes are a result and not the cause of disorders in which albuminuria is present, while Farquhar[34] believes that she now has studied enough pathologic material to say that the loss of foot processes is not associated just with albuminuria but occurs whenever the nephrotic syndrome is present, and is not found in the absence of nephrosis.

THE ENDOTHELIUM OF THE GLOMERULUS

The identity of the cell types seen in the normal glomerulus continues to provoke controversy among the electron microscopists. Everyone recognizes two cell types in the normal glomerular tuft: the epithelium of the glomerulus and a number of cells which are called endothelium. There are, however, some who believe that a third cell type exists in the area of the endothelial cells and have attributed to this "third" cell many of the manifestations of disease as it occurs in the glomerulus.

Buday,[19] in 1906, recognized two cell types—the endothelium and epithelium —and thought that he could differentiate them by their relation to the basement membrane. He believed that the glomerular epithelium lay to the capsular side of the membrane and that all other cells were endothelium. The ratio of endothelial cells to epithelial cells is frequently given by an investigator, and this varies between 10:1 and 1:10.[83] The significance of this ratio is somewhat unclear, and the reported value depends in great degree upon whether or not the investigator believes in the presence of the "third" cell type.

The question of whether or not a third cell exists in the glomerular stalk has not been answered by the electron microscopists, but considerable information has been gained regarding the size, shape, and position of the endothelial cell. In electron micrographs of the normal glomerulus only Yamada[124] and Policard[97] claim to be able to distinguish accurately three cell types—the epithelium, the endothelium, the "third" cell. All, however, rather well agree that the endothelial cell is shaped like a tube of fairly short length. On cross section it is "signet ring" shaped with a thin layer of cytoplasm extending around the capillary lumen from the mass of cytoplasm which contains the nucleus. The cytoplasm of the cell body proper, which Hall[52,54] called endoplasm, is seen in the areas of the stalk or axis which McManus[72] described so well. Only rarely can cell boundaries be found between adjacent endothelial cells, and this fact led Mueller[86] to postulate that the axial stalk consisted of a syncytium of endothelial cells, the peripheral portions of which were hollowed out into spaces forming the capillary lumens, and that this endothelial syncytium extending from the hilus actually was Zimmerman's mesangium or Kimmelstiel's and McManus' intercapillary space. Elias' diagrams[29] demonstrated this concept very clearly.

The thinned out portion of the endothelium lying adjacent to the basement membrane consists of two plasma membranes of 150 Å width, separated by a 200 to 300 Å cytoplasmic space. This membrane in some cross-section views appears to be discontinuous, as though it were perforated at fairly regular intervals. In coronal or tangential views in which the endothelial membrane appears en face, it frequently gives an appearance of "chicken wire fencing." This appearance initially led Hall to call it the *lamina fenestrata* and later, when there was some question as to whether or not the holes were artefacts or were truly present, he called it *lamina attenuata*.[54] Mueller[86] has called it the *endothelial lining network*. Rinehart,[105] in discussing the attenuated endothelial cytoplasm, believes that these interruptions represent small segments of cytoplasm devoid of fluid, or cytoplasmic vesicles involved in the transport of fluid, thus giving voice to a possibility that filtration might occur via the endothelial cytoplasm rather than

through openings in the endothelium. The size of these openings is rather variable—from 600 to 1,000 Å. This variation may well be dependent upon fixation, since the structure appears more prominent in tissue whose cellular cytoplasm appears fibrous and reticulated, than in micrographs in which the cytoplasm of cells appears to be a fairly homogeneous gel.

THE GLOMERULAR STALK

Zimmerman,[128] in 1933, propounded and explicitly described the "third" cell concept of the glomerulus. He rejected the idea that all cells within the confines of the basement membrane were endothelial cells because he found staining differences in this group of cells when he utilized the Golgi-Kopsch stain. In addition to an endothelial cell which bordered the capillary lumen and whose cell body usually lay on the stalk side of the lumen, he found a large pale cell which he thought was a fibrocyte, despite the fact that neither he nor any of the other anatomists had found collagen in the normal glomerulus. Zimmerman claimed that 25 to 35 per cent of the endothelial cells were in reality fibrocytes and that they formed a supporting stalk which stemmed from the hilus of the glomerulus. He labeled this stalk the *mesangium* and the fibrocytes *mesangial cells*. He stated that in man, as in all mammals investigated, a little tree of mesangium starts from the hilus, corresponds to the lobules, and is in contact with all of the capillaries. It was his belief that the mesangium, together with the basement membrane, formed an important intralobular supporting apparatus, and that without it the capillaries would have nothing to which to hang. Zimmerman agreed with all previous workers that little could be made out regarding the cytoplasm of the endothelial cell itself except that there is a nucleus and a small quantity of cytoplasm, usually adjacent to the mesangial cell. He observed that "capillaries free on all sides do not exist" in plane sections, and this observation led him to conclude that all of the capillaries were connected to each other and to the hilus by the mesangium (mesentery of blood vessels).

Von Moellendorff[83] stated, in 1927, that there were no cells in the glomerulus other than epithelial and endothelial. Later, under the influence of Zimmerman's observations,[128] he became convinced that connective tissue did exist. He[85] described a fine connective tissue structure in each glomerulus which branched from the hilus of the glomerulus and to which the capillaries were attached. He, however, expressed doubt that the quantity of "third" cells which Zimmerman saw was really present in the human glomerulus. He was unable to find any elastic fibers and concluded by saying that in each lobule there was a small core of connective tissue, on top of which sat the capillaries, and that both were covered with the *Deckzellen* (glomerular epithelium). He accepted Zimmerman's term *mesangium* for this small core of connective tissue and stated that, whenever it lay adjacent to the basement membrane, the mesangium and the membrane could not be distinguished from one another.

The anatomists who studied the glomerulus by the use of silver stains became interested in fibrils extending into the glomerulus from the hilus, apparently continuous with the silver-positive network surrounding the arterioles. Bensley[10] thought that endothelial cells extended into the glomerulus from the endothelium

of the afferent vessel. He felt that he had stained cell boundaries of the endothelial cells and that a thin layer of endothelium lay adjacent to the basement membrane within the glomerulus. He depicted silver-positive fibrils extending into the glomerulus and thought that these represented a stalk. McGregor,[68] in 1929, described the continuity of the endothelial cells of the tuft with those of the afferent and efferent vessels. She was unable to stain any cell boundaries of endothelial cells and held that some connective tissue cells might be present. In a second article,[69] she depicted intercapillary hyaline fibers at the site of the mesangium as one of the changes which occurred in glomerulonephritis, but paid little attention to the stalk or the mesangium concept as such. MacCallum,[78] in 1934, reported that in the normal glomerulus special attention was required to recognize the few connective tissue cells between the capillaries. He felt that glomerular injury was followed by connective tissue proliferation and, since it was proliferation of the connective tissue rather than an increase in endothelium which eventually caused capillary obstruction, nephritis must be intercapillary rather than intracapillary.

Kimmelstiel and Wilson,[65] in 1936, brought the whole problem of intracapillary versus intercapillary disease to the fore by describing a group of eight cases of diabetic nephrosis as "intercapillary glomerulosclerosis." Their description rests upon MacCallum's concept of intercapillary versus intracapillary disease, and upon Zimmerman's concepts that a stalk of fibrocytes (mesangium) exists in each lobule and that there are two basement membranes. Kimmelstiel and Wilson believed that hyaline material extended into the tuft from the efferent vessel and that a broadening and splitting of the capillary basement membrane occurred in addition to an accumulation of intercapillary hyaline fibers. Since the work of Kimmelstiel and Wilson attracted attention to the "intercapillary space," much has been written regarding the diseases which involve it. McManus[72] has consistently and clearly described this space as a position within the confines of the basement membrane, occupied by cells of unknown nature, probably endothelial. He[71] developed and popularized the Schiff's P.A.S. stain to demonstrate the glomerular basement membrane and described the capillary loop as curving around a central axis, with the basement membrane covering both the capillary loop (lumen) and the axial space intervening between the loops. This space always contained either cytoplasm or the nucleus (or both) of an endothelial cell. In some cases, the basement membrane appeared thickened at the site in which it lay adjacent to the axial space, producing one variety of axial thickening. McManus stated that the nuclei of these axial cells stained like endothelial cells, but he could not identify them with certainty and called them "intercapillary" or "third" cells, feeling that they were probably the cells described by Zimmerman as fibrocytes or by Goormaghtigh[43] as muscle cells which controlled glomerular tone. McManus[77] recognized that these stalk cells increased in number or were invaded by other cell types in nephritis and that a decrease in the cellular mass of the stalk occurred in renal ischemia, giving the glomerulus an "open" appearance.

Observations on glomeruli which are the site of disease indicate that a foreign substance may be interposed between the endothelium and the basement mem-

brane. When this occurs the endothelium loses its fenestrated appearance,[87] and Jones[62,63] notes that it will stain with special silver stains, thus giving the impression of two basement membranes. Jones also feels that there is a special type of connective tissue in the glomerular stalk. He claims that the mesangial tissue is surrounded by silver-positive fibrillar tissue of an irregular, spongy nature. This tissue stains in a fashion similar to that of the basement membrane and has qualities which make it appear different from other fibrillary connective tissue. He feels that fibromucin is an appropriate term for this material.

The "third" cell or mesangial cell is called an *intercapillary* cell by Yamada.[124] He, also, commented on the spongy fingers of basement membrane material which are present at the sites where the basement membrane is in contact with the endothelial or "third" cells. Thickening of the basement membrane at this point has been noted by all of the histologists. Fingerlike projections extending from the basement membrane around and through the cells of the stalk are present in the electron micrographs of most observers, although Yamada is the first to bring attention to them. Hall attributed such views to tangential sections of wrinkled basement membranes, as did Mueller.[86] In one portion of his work, Yamada[124] described a continuous basement membrane in the glomerulus, which enclosed the glomerular capillaries almost completely except at the inner (stalk) side of the capillary loop. Here he felt that the basement membrane was often lacking or incomplete and that the epithelium might then come into direct contact with the endothelium or "third" cell. No other workers have noted this discontinuity in the basement membrane. In the cytoplasm of the intercapillary cell Yamada[124] recognized mitochondria, reticulum, vesicles, and numerous delicate filaments which suggested a similarity to smooth muscle cells. The characteristic fibrillar nature of these cells permitted Yamada to distinguish them from endothelial cells. He described small processes which extended from these cells to the capillary lumens, there forming *intracapillary colliculi*. Electron micrographs of other workers do not show the clear-cut distinctions between endothelial cells and intercapillary cells which Yamada describes, and a review of his published electron micrographs shows the differences between endothelial and "third" cells to be less apparent than his description indicates.

Elias[28,29] made drawings of his concept of lobular structure based upon data obtained by axis measurements of the capillary lumens. He believes that a multifingered mass of cells extends into the glomerulus from the hilus and that within this mass of cells—probably a syncytium—there is a multitude of anastomosing channels—the capillary lumens. The cell bodies, or portions containing the nucleus, lie in the central portion of the stalk, while the outer portions of this cell mass are thin and attenuated and form the attenuated endothelium adjacent to the basement membrane. Overlying this mass of cells and lumens is a continuous sheet of basement membrane, continuous at the hilus with the basement membrane of Bowman's capsule. He has labeled this mass of cells the *endenchyma*. In reality, his endenchyma is the same glomerular stalk made of endothelial cells that was described by Mueller and Hall. The importance of his contribution lies in his having focused attention upon the cell mass—whether or not it is a syncytium—and the relative de-emphasis of the importance of the capillary lumen and its outer wall.

Within the past few months reports have begun to appear indicating an attack upon glomerular pathology by the electron microscopists. Farquhar[31,32,33] has begun to describe the anatomic differences between the nephroses, in which epithelial alterations are present, and the nephritides in which glomerular stalk, endothelial, and basement membrane changes can be seen. Piel[95,96] and Reid[99] have made attempts to study experimental glomerular disease with the electron microscope and much more work in this area is undoubtedly forthcoming. Newer staining techniques have recently been employed and in the years immediately ahead much information will certainly be uncovered by the use of phase microscopy. Soon, too, accurate descriptions of human glomerular pathology should be available through the use of renal punch biopsy and a combination of phase and electron microscopy.

COMPONENTS OF THE GLOMERULUS

Basement membrane of Bowman's capsule—homogeneous membrane extending from the basement membrane of the proximal convoluted tubule to the glomerular hilus

Basement membrane of the glomerulus—homogeneous membrane enclosing the glomerular endothelium, the capillary lumens, and the (?) "third" cells

Epithelium of Bowman's capsule—single layer of flattened cells lining the interior of the basement membrane of Bowman's capsule.

Epithelium of glomerulus—(podocyte, Hall; epicyte, Clara; Deckzellen, Zimmerman) atrocyte-shaped cell with many arms or trabeculae overlying the basement membrane of the glomerulus

trabecula—a large arborization from the cell body of glomerular epithelium

foot process—(pedicel, Hall) terminal twigs of a trabecula of glomerular epithelium which interdigitate with foot processes of other trabeculae

Juxtaglomerular apparatus—(polkissen cells, Zimmerman) granular cells in the media of the afferent artery as it enters Bowman's capsule

Endothelium of the glomerulus—(endenchyma, Elias) cells whose bodies and nuclei lie in or comprise the glomerular stalk and whose outer portions contain the capillary lumens

attenuated endothelial cytoplasm—(lamina fenestrata, Hall; lamina attenuata, Hall; endothelial lining network, Mueller) that portion of endothelium beneath the glomerular basement membrane through which filtration occurs

Bowman's capsule—expanded end of the nephric tubule enclosing the glomerular tuft—made up of epithelium and basement membrane (the terms "parietal" and "visceral" layers of Bowman's capsule have been discarded)

Glomerular tuft—(Malpighian corpuscle, Bowman) the ball-shaped capillary rete extending between the afferent and efferent arteries—composed of glomerular endothelium, epithelium, basement membrane, and (?) "third" cell

Glomerular stalk—(mesangium, Zimmerman; axial space, McManus; intercapillary space, Kimmelstiel and Wilson, MacCallum; endenchyma, Elias) the contiguous group of cells, or syncytium, extending from the hilus, becoming branched in nature; with capillary lumens in the periphery of this cellular mass

Glomerular capillary—unable to be defined in a way that is applicable to a majority of publications

Capillary lumen—the space in which blood cells and plasma circulate

Capillary wall—by light microscopy this probably is composed of glomerular epithelial foot processes, glomerular basement membrane, and the attenuated portion of glomerular endothelium

Capillary loop—by some authors, a single sinuous unbranched vessel, which extends from afferent to efferent artery; by most authors, any capillary as it courses into and out of Bowman's capsule, dividing and reuniting—usually implies capillary lumen, attenuated endothelium, basement membrane, and epithelium

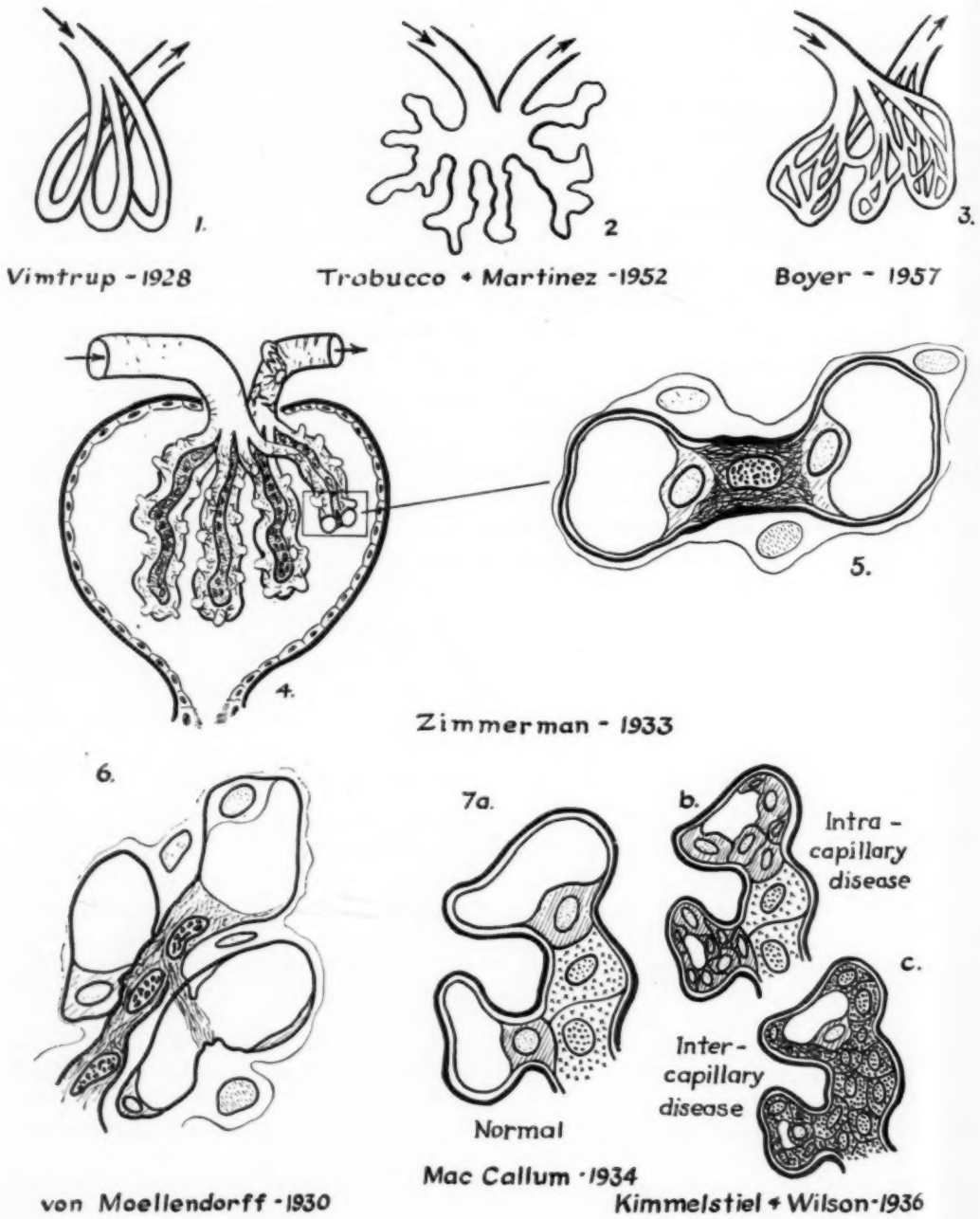


Fig. 1.—*1, 2, 3,* **Diagrammatic representation of concepts of organization of the capillaries of the glomerular tuft.** *4, 5,* **A descriptive drawing by Zimmerman, showing his concept that the single capillary loops are bound together by the interstitial tissue mass.** *6,* **Drawing made from von Moellendorff's idea that the interstitial cell mass held the capillaries together by attaching to the external portion of the basement membrane.** *7a,* **A concept of the glomerular stalk described by MacCallum, who believed in the presence of a "third" cell.** *7b,* **The mechanism of capillary lumen obliteration by proliferation of the endothelium.** *7c,* **The mechanism of capillary lumen obliteration by proliferation of the "third" cell, whose position is between the capillaries—i.e., between the capillary lumens and endothelial cell of two capillaries. Note that should there exist but one cell type in the glomerular stalk, there can be no distinction between intra- and intercapillary disease.**

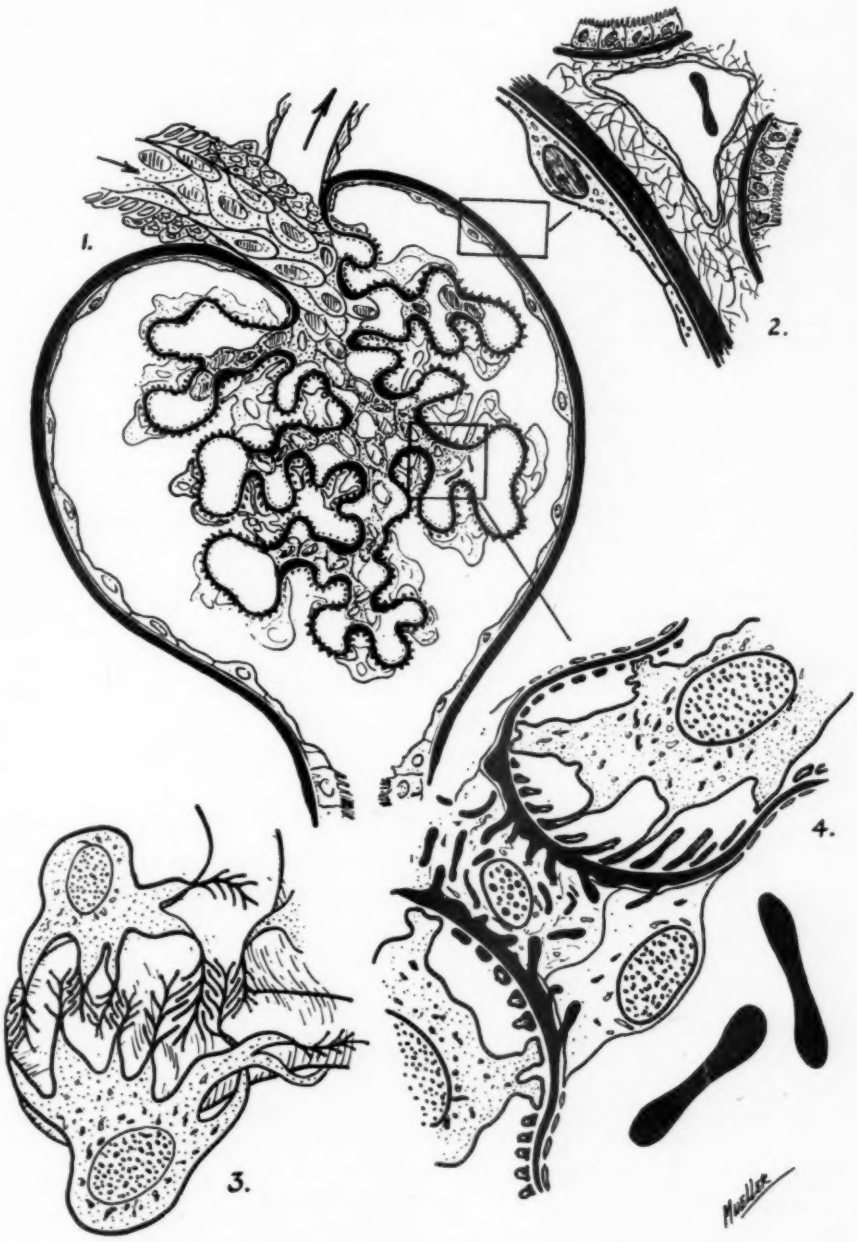


Fig. 2.—*1*, A diagram of the glomerulus seen in plane section. The afferent arteriole is shown surrounded by the polkissen cells, and the endothelium enters the tuft in an uninterrupted stream of cells. This drawing implies that the entire stalk is endothelium and denies the "third" cell, although the latter's position would be within the cellular mass of the stalk if it does exist. *2*, An enlarged portion of Bowman's capsule showing the outer zone of reticular fibrils extending to endothelium of a peritubular capillary and to the basement membranes of two proximal convoluted tubules. *3*, The exterior of a knuckle of capillary, covered with basement membrane, on which are situated two epithelial cells. A few trabeculae and interdigitating foot processes are shown. *4*, An enlargement of the intercapillary space showing the presence of a "third" cell and an endothelial cell. The spongy fingers of basement membrane in and around these cells are shown. It is the author's belief that the "third" cell depicted here is probably an endothelial cell whose lumen is in a plane above or below that of the plane of the paper, and that in third dimensional reconstruction this cell would relate to a capillary lumen connecting the lumens existing at the right and left portions of this drawing.

REFERENCES

1. Allen, A. C.: Arch. Path. **32**:33, 1941.
2. Allen, A. C.: The Kidney, Medical and Surgical Diseases, New York, 1951, Grune & Stratton, Inc.
3. Allen, A. C.: Am. J. Med. **18**:277, 1955.
4. Allen, R. B.: Anat. Rec. **34**:41,1926.
5. Allen, R. B.: Anat. Rec. **35**:30, 1927.
6. Bargmann, A., Knoop, A., and Schiebler, T. H.: Ztschr. f. Zellforsch. u. mikro. Anat. **42**:386, 1955.
7. Bargmann, W.: Ztschr. f. Zellforsch. u. mikro. Anat. **8**:765, 1929.
8. Bell, E. T.: Renal Diseases, Ed. 2, Philadelphia, 1950, Lea & Febiger.
9. Bensley, R. R., and Vimtrup, B.: Anat. Rec. **39**:37, 1928.
10. Bensley, R. D.: Am. J. Anat. **44**:141, 1929.
11. Bensley, R. R., and Bensley, R. D.: Anat. Rec. **47**:147, 1930.
12. Bergstrand, A.: Lab. Invest. **6**:191, 1957.
13. Bohle, A., and Krecke, H-J.: Virchows Arch. **327**:663, 1955.
14. Borst, J. G. G.: Ztschr. mikro. anat. Forsch. **23**:455, 1931.
15. Bowman, W.: Philos. Tr. Royal Soc. London **132**:57, 1842. Reprinted in Medical Classics **5**:249, 1940-41.
16. Boyer, C. C.: Anat. Rec. **121**:427, 1955.
17. Boyer, C. C.: Anat. Rec. **125**:433, 1956.
18. van Breeman, V. L., Reger, J. F., and Cooper, W. G.: J. Biophys. and Biochem. Cytology **2**: (Supp.) 283, 1956.
19. Buday, K.: Virchows Arch. Path. Anat. **186**:145, 1906.
20. Chrzonszczewsky, N.: Virchows Arch. Path. Anat. **31**:153, 1864.
21. Clara, M.: Ztschr. mikro. anat. Forsch. **40**:147, 1936.
22. Corner, G. W.: Contr. Embryol. Carnegie Inst. **9**:87, 1920.
23. Crabtree, C. E.: Endocrinology 29:204, 1941.
24. Dalton, A. J., Kahler, H., Striebich, M. J., and Lloyd, B.: J. Nat. Cancer Inst. **11**:439, 1950-51.
25. Dalton, A. J.: J. Nat. Cancer Inst. **11**:1163, 1950-51.
26. Dalton, A. J., Kahler, H., and Lloyd, B. J.: Anat. Rec. **111**:67, 1951.
27. Ehrich, W., and Piel, C.: Proc. Fifth Ann. Conf. on Nephrotic Syndrome, New York, 1953, National Nephrosis Foundation, pp. 117-134.
28. Elias, A. H.: Research in the Service of Medicine—(Searle) **46**:3, 1956.
29. Elias, A. H.: Anat. Anzeig. **104**:26, 1957.
30. Elias, A. H., and Bortner, S.: Chicago Med. School Quarterly **18**:11, 1957.
31. Farquhar, M. G., Vernier, R. L., and Good, R. A.: Schweiz. med. Wchnschr. **17**:501, 1957.
32. Farquhar, M. G., Vernier, R. L., and Good, R. A.: Am. J. Path. **33**:791, 1957.
33. Farquhar, M. G., Vernier, R. L., and Good, R. A.: J. Exper. Med. **106**:649, 1957.
34. Farquhar, M. G.: Personal communication, 1957.
35. Fawcett, D.: Anat. Rec. **120**:733, 1954.
36. Gautier, A., Bernhard, W., and Oberling, C.: Societé de Biologie, Paris, Comptes Rendues des Seances **144**:1605, 1950.
37. Gerlach, J.: Arch. f. Anat., Physiol. u. Wissensch. Med. pp. 102-112, 1848.
38. Gersh, I., and Catchpole, H. R.: Am. J. Anat. **85**:457, 1949.
39. Goormaghtigh, N.: J. Physiol. **90**:63P, 1937.
40. Goormaghtigh, N., and Handovsky, H.: Arch. Path. **26**:1144, 1938.
41. Goormaghtigh, N.: Am. J. Path. **16**:409, 1940.
42. Goormaghtigh, N.: Am. J. Path. **23**:513, 1947.
43. Goormaghtigh, N.: J. d'urol. **57**:569, 1951.
44. Gruenwald, P., and Popper, H.: J. Urol. **43**:452, 1940.
45. Hall, B. V., Roth, E., and Johnson, V.: Anat. Rec. **115**:427, 1953.
46. Hall, B. V., Roth, E., and Johnson, V.: Anat. Rec. **115**:315, 1953.
47. Hall, B. V.: Fed. Proc. **12**:467, 1953.
48. Hall, B. V., and Roth, L. E.: J. Appl. Physics **24**:1424, 1953.
49. Hall, B. V.: Proc. Fifth Ann. Conf. on Nephrotic Syndrome, New York, 1953, National Nephrosis Foundation, pp. 1-39.
50. Hall, B. V.: Anat. Rec. **118**:425, 1954.
51. Hall, B. V., and Roth, E.: Anat. Rec. **120**:733, 1954.
52. Hall, B. V.: Proc. Sixth Ann. Conf. on Nephrotic Syndrome, New York, 1954, National Nephrosis Foundation, pp. 1-21.
53. Hall, B. V.: J. Histochem. **3**:310, 1955.
54. Hall, B. V.: Am. J. Path. **32**:646, 1956.
55. Hartroft, P. M., and Hartroft, W. S.: J. Exper. Med. **97**:415, 1953.
56. Hartroft, P. M., and Hartroft, W. S.: J. Exper. Med. **102**:205, 1955.
57. Huber, G. C.: The Harvey Lectures, 1909-10, pp. 100-149.

58. Irvine, E., Rinehart, J. F., Mortimore, G. E., and Hopper, J., Jr.: Am. J. Path. **32**:647, 1956.
59. Johnston, W. B.: Anat. Anzeig. **16**:260, 1899.
60. Jones, D. B.: Am. J. Path. **27**:991, 1951.
61. Jones, D. B.: Am. J. Path. **29**:33, 1953.
62. Jones, D. B.: Am. J. Path. **33**:313, 1957.
63. Jones, D. B.: Personal communication, 1957.
64. Kimmelstiel, P.: Am. J. Path. **11**:483, 1935.
65. Kimmelstiel, P., and Wilson, C.: Am. J. Path. **12**:83, 1936.
66. Kulenkampff, H.: Ztschr. f. Anat. u. Entwick. **117**:520, 1954.
67. Ludwig, C.: The Kidney, *in* Stricker's Manual of Human and Comparative Histology, Vol. 2, London, 1872, Sydenham Society.
68. McGregor, L.: Am. J. Path. **5**:545, 1929.
69. McGregor, L.: Am. J. Path. **5**:559, 1929.
70. McGregor, L.: Am. J. Path. **6**:347, 1930.
71. McManus, J. F. A.: Am. J. Path. **24**:643, 1948.
72. McManus, J. F. A.: Am. J. Path. **24**:1259, 1948.
73. McManus, J. F. A.: Proc. American Diabetes Assn. **9**:303, 1949.
74. McManus, J. F. A.: Medical Diseases of the Kidney, Philadelphia, 1950, Lea & Febiger.
75. McManus, J. F. A., Lupton, C. H., Jr., and Graham, L. S., Jr.: Anat. Rec. **110**:57, 1951.
76. McManus, J. F. A.: Am. J. Path. **30**:640, 1954.
77. McManus, J. F. A.: Am. J. Path. **31**:589, 1955.
78. MacCallum, W. S.: Bull. Johns Hopkins Hosp. **55**:416, 1934.
79. Mall, F. P.: Rep. Johns Hopkins Hospital **1**:171, 1896.
80. Mall, F. P.: Bull. Johns Hopkins Hosp. **12**:133, 1901.
81. Mall, F. P.: Am. J. Anat. **1**:329, 1901-2.
82. Malpighi, M.: De Viscerum Structura, 1669, quoted by Bowman, 1842.[15]
83. von Moellendorff, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **6**:441-450, 1927.
84. von Moellendorff, W.: Ztschr. f. Zellforsch. u. mikr. Anat. **11**:46, 1930.
85. von Moellendorff, W.: Handbuch der Mikroskopischen Anatomie. Teil 7[1], Berlin, 1930.
86. Mueller, C. B., Mason, A. D., Jr., and Stout, D. G.: Am. J. Med. **18**:267, 1955.
87. Mueller, C. B.: Unpublished information.
88. Oberling, C., Gautier, A., and Bernhard, W.: Presse méd. **59**:938, 1951.
89. Pease, D. C., Baker, R. F., and Warren, O.: Bull. Univ. Southern California Med. **2**:9, 1950.
90. Pease, D. C., and Baker, R. F.: Am. J. Anat. **87**:349, 1950.
91. Pease, D. C.: Anat. Rec. **118**:339, 1954.
92. Pease, D. C.: Anat. Rec. **121**:701, 1955.
93. Pease, D. C.: Anat. Rec. **121**:723, 1955.
94. Pease, D. C.: J. Histochem. **3**:295, 1955.
95. Piel, C. F., Dong, L., Modern, F. W. S., Goodman, J. R., and Moore, R.: J. Exper. Med. **102**:573, 1955.
96. Piel, C. F., Dong, L., Goodman, J. A., and Moore, R.: A.M.A. Am. J. Dis. Child. (In Press), 1957.
97. Policard, A., Collet, A., and Giltaire-Ralyte, L.: Arch. Anat. Micro. **44**:1, 1955.
98. Reid, R. T. W.: Australian J. Exper. Biol. & M. Sc. **32**:235, 1954.
99. Reid, R. T. W.: Australian J. Exper. Biol. & M. Sc. **34**:143, 1956.
100. Rhodin, J.: Correlation of Ultrastructural Organization and Function in Normal and Experimentally Changed Proximal Convoluted Tubule Cells of the Mouse Kidney, Stockholm, 1954, Artiebolaget Godvil (private printing).
101. Rhodin, J.: Exper. Cell Res. **8**:572, 1955.
102. Rinehart, J. F., Farquhar, M. G., Jung, H. C., and Abul-Haj, S. K.: Am. J. Path. **29**:21, 1953.
103. Rinehart, J. F., and Farquhar, M. G.: J. Appl. Physics **25**:1463, 1954.
104. Rinehart, J. F., Farquhar, M. G., and Gould, E.: Am. J. Path. **31**:587, 1955.
105. Rinehart, J. F.: A.M.A. Arch. Path. **59**:439, 1955.
106. Rühle, G.: Arch. f. Anat. u. Entwick. pp. 153-170, 1897.
107. Russakoff, A.: Beitr. path. Anat. u. z. allg. Path. **45**:476, 1908.
108. Ruyter, J. H. C.: Ztschr. f. Zellforsch. u. mikro. Anat. **2**:242, 1925.
109. Sakaguchi, H.: Keio J. Med. **4**:103, 1955.
110. Schumlansky, A.: Anatomicam de renum structura, Argentorati, 1782, Quoted by Bowman, 1842.[15]
111. Selye, H.: J. Urol. **42**:637, 1939.
112. Simer, P. H.: Anat. Rec. **118**:409, 1954.
113. Simer, P. H., Kirschbaum, A., and Mahon, E. S.: Anat. Rec. **115**:440, 1953.
114. Simer, P. H.: Anat. Rec. **121**:416, 1955.
115. Trabucco, A., and Marquez, F.: J. Urol. **67**:235, 1952.
116. Vernier, R. L., Farquhar, M. G., Brunson, J. G., and Good, R. A.: J. Lab. & Clin. Med. **48**:951, 1956.

117. Vernier, R. L., Farquhar, M. G., Brunson, J. G., and Good, R. A.: J. Clin. Invest. **35**:741, 1956.
118. Vernier, R. L., Farquhar, M. G., Brunson, J. G., and Good, R. A.: Electron Microscopic Pathology of the Various Forms of the Nephrotic Syndrome, A.M.A. Am. J. Dis. Child, 1957-58. (In Press.)
119. Vimtrup, B.: Am. J. Anat. **41**:123, 1928.
120. Volterra, M.: Ztschr. f. Zellforsch. u. mikro. Anat. **7**:135, 1928.
121. Wilbur, D. L.: Arch. Path. **12**:413, 1931.
122. Wilmer, H. A.: Anat. Rec. **80**:507, 1941.
123. Yamada, E.: J. Histochem. **3**:309, 1955.
124. Yamada, E.: J. Biophysics and Biochem. Cytol. **1**:551, 1955.
125. Zimmerman, K. W.: Anat. Anzeig. **48**:335, 1915.
126. Zimmerman, K. W.: Ztschr. f. Anat. u. Entwick. **68**:29, 1923.
127. Zimmerman, K. W.: Ztschr. mikro. anat. Forsch. **18**:520, 1929.
128. Zimmerman, K. W.: Ztschr. mikro. anat. Forsch. **32**:176, 1933.

Announcements

THE FOURTEENTH BRAZILIAN CONGRESS OF CARDIOLOGY was held in Rio de Janeiro, from July 7 to 13, 1957.

In the General Assembly it was decided that the place in Brazil for the 1960 Inter-American Meeting will be the city of Rio de Janeiro, under the chairmanship of Prof. Magalhães Gomes.

The new directory for the Brazilian Society of Cardiology for 1957-1958 was elected, as follows: President—Dr. A. de Carvalho Azevedo; Vice President—Prof. Rubens Maciel; General Secretary—Dr. Robison Roubach; Treasurer—Dr. G. Strunck; Sub-Secretary—Dr. Adão Mattos.

The ELEVENTH ANNUAL POSTGRADUATE COURSE ON DISEASES OF THE CHEST will be sponsored by the Council on Postgraduate Medical Education of the American College of Chest Physicians, at the Warwick Hotel, Philadelphia, March 3-7, 1958.

The most recent advances in the diagnosis and treatment of chest diseases—medical and surgical—will be presented. The tuition fee is $75, including round-table luncheons.

Further information may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Ill.

The first meeting in America of the INTERNATIONAL CONGRESS OF INTERNAL MEDICINE will be held in Philadelphia, April 23-26, 1958. This meeting was arranged after an invitation was officially extended by the American College of Physicians. It is intended to encourage greater participation of American physicians in the International Society and to give foreign members a first-hand opportunity to learn more about American developments in the medical sciences.

The Association numbers 4,000 members (1,900 American physicians) from 34 nations of the world. These include many members from behind the so-called iron curtain, and scores of registrants will attend from Russia and neighboring countries.